Drug Eruptions - When to Worry

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I have no conflicts of interest to disclose
I may be discussing off-label use of medications

Drug reactions:
3 things you need to know

1. Type of drug reaction
2. Statistics:
   - Which drugs are most likely to cause that type of reaction?
3. Timing:
   - How long after the drug started did the reaction begin?

Drug Eruptions: Degrees of Severity

<table>
<thead>
<tr>
<th>Simple</th>
<th>Complex</th>
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</thead>
<tbody>
<tr>
<td>Morbilliform drug eruption</td>
<td>Drug hypersensitivity reaction</td>
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<tr>
<td></td>
<td>Stevens-Johnson syndrome (SJS)</td>
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<tr>
<td></td>
<td>Toxic epidermal necrolysis (TEN)</td>
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<tr>
<td>Minimal systemic symptoms</td>
<td>Systemic involvement</td>
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<tr>
<td></td>
<td>Potentially life threatening</td>
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</tbody>
</table>

Common Causes of Cutaneous Drug Eruptions

- Antibiotics
- NSAIDs
- Sulfa
- Allopurinol
- Anticonvulsants
Morbilliform (Simple) Drug Eruption

- Begins 5-10 days after drug started
- Erythematous macules, papules
- Pruritus
- No systemic symptoms
- Risk factors: EBV, HIV infection
- Treatment:
  - D/C medication
  - Diphenhydramine, topical steroids
- Resolves 7-10 days after drug stopped
  - Gets worse before gets better

Drug Induced Hypersensitivity Syndrome

- Skin eruption associated with systemic symptoms and alteration of internal organ function
- “DRESS” - Drug reaction w/ eosinophilia and systemic symptoms
- “DIHS” = Drug induced hypersensitivity syndrome
- Begins 2-6 weeks after medication started
  - time to abnormally metabolize the medication
- Role for viral reactivation, esp HHV6
- Mortality 10%

Hypersensitivity Reactions

Drugs

- Aromatic anticonvulsants
  - Phenobarbital, carbamazepine, phenytoin
  - THESE CROSS-REACT
- Sulfonamides
- Lamotrigine
- Dapsone
- Allopurinol (HLA-B*5801)
- NSAIDs
- Other
  - Abacavir (HLA- B*5701)
  - Nevirapine (HLA-DQB1*0101)
  - Minocycline, metronidazole, azathioprine, gold salts
- Each class of drug causes a slightly different clinical picture

Drug Induced Hypersensitivity Syndrome

- Each class of drug causes a slightly different clinical picture
- Facial edema characteristic of all
- Anticonvulsants:
  - 3 weeks
  - Atypical lymphocytosis, hepatic failure
- Dapsone:
  - 6 weeks
  - No eosinophilia
- Allopurinol:
  - 7 weeks
  - Elderly patient on thiazide diuretic
  - Renal failure
  - Requires steroid sparing agent to treat (avoid azathioprine)
DIHS- Clinical Features

- Rash
  - FACIAL EDEMA
- Fever (precedes eruption by day or more)
- Pharyngitis
- Hepatitis
- Arthralgias
- Lymphadenopathy
- Hematologic abnormalities
  - eosinophilia
  - atypical lymphocytosis
- Other organs involved
  - Interstitial pneumonitis, interstitial nephritis, thyroiditis
  - Myocarditis- acute eosinophilic myocarditis or acute necrotizing eosinophilic myocarditis
  - EKG, echocardiogram, cardiac enzymes

Hypersensitivity Reactions Treatment

- Stop the medication
- Follow CBC with diff, LFT’s, UA w micro, BUN/Cr
- Avoid cross reacting medications!!!!
  - Aromatic anticonvulsants cross react (70%)
    - Phenobarbital, Phenytoin, Carbamazepine
    - Valproic acid and Keppra generally safe
- Systemic steroids (Prednisone 1.5-2mg/kg)
  - Taper slowly- 1-3 months
- Allopurinol hypersensitivity- requires steroid-sparing agent
  - NOT azathioprine (also metabolized by xanthine oxidase)
- Completely recover, IF the hepatitis resolves
- Check TSH monthly for 6-9 months
- Watch for later cardiac involvement (low EF)

Severe Bullous Reactions

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

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

- Medications
  - Sulfonamides
  - Aromatic anticonvulsants (carbamazapine [HLA-B*1502], phenobarbital, phenytoin)
  - Allopurinol (HLA-B*5801)
  - NSAIDs (esp Oxicams)
  - Nevirapine (HLA-DRB1*0101)
  - Lamotrigine
  - Weaker link: Sertraline, Pantoprazole, Tramadol

Stevens-Johnson (SJS) versus Toxic Epidermal Necrolysis (TEN)

<table>
<thead>
<tr>
<th>Disease</th>
<th>BSA</th>
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<tbody>
<tr>
<td>SJS</td>
<td>&lt; 10%</td>
</tr>
<tr>
<td>SJS/TEN overlap</td>
<td>10-30%</td>
</tr>
<tr>
<td>TEN with spots</td>
<td>&gt; 30%</td>
</tr>
<tr>
<td>TEN without spots</td>
<td>Sheets of epidermal loss &gt; 10%</td>
</tr>
</tbody>
</table>
SJS/TEN: Emergency Management

- Stop all unnecessary medications
  - The major predictor of survival and severity of disease
- Ophthalmology consult
- Check for Mycoplasma- 25% of SJS in pediatric patients
- Treat like a burn patient
  - Monitor fluid and electrolyte status (but don’t overhydrate)
  - Nutritional support
  - Warm environment
  - Respiratory care
- Death (up to 25% of patients with more than 30% skin loss, age dependent)

SJS/TEN: Treatment

- Topical
  - Protect exposed skin, prevent secondary infection
  - Aquaphor and Vaseline gauze
- Systemic- controversial
  - No role for empiric antibiotics
  - Surveillance cultures
  - Treat secondary infection (septicemia)
  - Consider antivirals, treat Mycoplasma if present
- SJS: high dose corticosteroids -1.5-2 mg/kg prednisone (no RCT)
- TEN
  - IVIG 1g/kg/d x 4d
  - TNF blockade, cyclosporine

Unique Drug Eruptions
Consult: 2 days of redness, pustules, neutrophilia on azithromycin for bronchitis

Acute generalized exanthematous pustulosis
Clinical Features

• Acute onset
• Fever, neutrophilia
• Edema (face, hands)
• Additional morphologies
  – purpura, vesicles, bullae, erythema multiforme-like lesions
• Mucous membrane lesions!
• May mimic pustular psoriasis
• Typically resolves within 2 weeks of stopping medication, but may require systemic steroids

Acute Generalized Exanthematous Pustulosis = Pustular Drug Eruption

• EuroSCAR (97 cases of AGEP, 1009 controls):
  – Macrolides
  – Ampicillin/amoxicillin
  – Quinolones
  – (hydroxy)chloroquine
  – Sulphonamides
  – Terbinafine
  – Diltiazem
  – No infections found
  – Not associated with personal or family history of psoriasis

• Mercury
• Enterovirus infection
Consult: 5 days of painful red lesion after taking tylenol for headache

Amantadine

Fixed Drug Eruption

- Morphology
  - Annular red plaque
  - Can have central bulla
  - Heals with marked hyperpigmentation
- Pain is the major symptom
- Limited number of lesions
- “Fixed” is a curious phenomenon
  - if patient takes the same medication again, the same spots light up
- Spontaneously resolves

Consult: Blisters after starting vancomycin

Drug-Induced Linear IgA Disease

- Immune-mediated subepidermal blistering disease
  - Antigen: 97 kDa of BPAG2 (BP180)
  - DIF: band-like (linear) IgA deposition at DEJ
- Clinical features
  - Subepidermal blisters accentuated in flexural areas
  - Morphology: herpetiform or rosette-like
- Can be caused by medications
  - Vancomycin most common
- Spontaneously resolves after stopping medication in most cases
### Drug-Induced Linear IgA Disease

- **Common causes**
  - Vancomycin
  - Penicillins
  - Cephalosporins
  - Captopril

- **Others**
  - Amiodarone
  - Sulfamethoxazole
  - Diclofenac
  - Furosemide
  - Glyburide
  - GCSF
  - IFN
  - Lithium
  - Phenytoin
  - Piroxicam
  - Rifampin

### Photosensitivity Reactions

- A combination of the medication and sun exposure are required to induce the reaction
- May occur many months after the medication has been started (since sun exposure may be variable)
- May occur through window glass (UVA)

Consult: Started doxycycline for rosacea 2 mo ago, then went to Maui for a conference
Photosensitivity Reactions

Etiology

- Sulfonamides
  - Antibiotics (TMP/SMX)
  - Thiazide diuretics (HCTZ!!!)
- Tetracyclines
  - Tetra>Doxy>Minocin
- Anti-inflammatories: NSAIDs
  - Piroxicam > Naproxen > Ibuprofen

Photosensitivity Reaction

- Pruritus, erythema, and scaling in sun exposed areas of the face, “vee of neck”, dorsal forearms and arms
- Over time may spread to involve protected areas
- May continue after the medication has been stopped

NSAID Photosensitivity

- Blistering eruption at periphery and dorsal hand is characteristic
- May be no eruption elsewhere
Photosensitivity Eruptions
Treatment
• Stop the suspected medication
• Sun Protection/Avoidance
• UVA sunblock (zinc or titanium dioxide)
• Topical Steroids
• Antihistamines

Summary- Signs of a Serious Drug Eruption
• Facial edema (DRESS/DIHS)
• Skin pain
• Blisters (widespread)
• Eosinophilia
• Transaminitis
• Renal involvement (check UA)