Goals of this lecture

- Drug eruptions
  - Tell the difference between a benign and serious drug eruption
  - Know which drug(s) to stop
- The red leg
  - Recognize the mimics of cellulitis
- Pyoderma gangrenosum
  - Avoid a potential disaster

Case

- 46 year old HIV+ man admitted to ICU for r/o sepsis
- Severely hypotensive → IV fluids, norepinephrine
- Sepsis? → antibiotics are started
- At home has been taking trimethoprim/sulfamethoxazole for UTI
Per the drug chart, the most likely culprit is:

<table>
<thead>
<tr>
<th>Day -&gt;</th>
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Rash onset
Admit day

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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<tbody>
<tr>
<td>Morbilliform drug eruption</td>
<td>Drug hypersensitivity reaction</td>
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<tr>
<td>Stevens-Johnson syndrome (SJS)</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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<td>Potentially life threatening</td>
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</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

Simple drug eruption- day 1

Simple drug eruption- day 3
Simple drug eruption - day 7

Hypersensitivity Reactions

Skin eruption associated with systemic symptoms and alteration of internal organs

“DRESS” - Drug reaction w/ eosinophilia and systemic symptoms

Begins 2-6 weeks after medication started
  - time to abnormally metabolize the medication

Mortality 10-25%

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-DRB1*0101)
  - Minocycline, metronidazole, azathioprine, gold salts

Each class of drug causes a slightly different clinical picture

Hypersensitivity Reactions

Clinical features

- Rash
- Fever (precedes eruption by day or more)
- Pharyngitis
- Hepatitis
- Arthralgias
- Lymphadenopathy
- Hematologic abnormalities
  - eosinophilia
  - atypical lymphocytosis
- Other organs involved
  - myocarditis, interstitial pneumonitis, interstitial nephritis, thyroiditis
Hypersensitivity Reactions- Treatment

- Stop the medication
- Follow CBC with diff, LFT’s, 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 may require steroid sparing agent
  - NOT azathioprine (also metabolized by xanthine oxidase)
- Completely recover, IF the hepatitis resolves
- Check TSH monthly for 6 months
- Watch for later cardiac involvement (low EF)

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>
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<tr>
<td>SJS/TEN overlap</td>
<td>10-30%</td>
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<tr>
<td>TEN “with spots”</td>
<td>&gt; 30%</td>
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<tr>
<td>TEN “without spots”</td>
<td>Sheets of epidermal loss &gt; 10%</td>
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</table>

Atypical targets: Mucosal membranes ≥ 2

Causes: Drugs
Mycoplasma
HSV

Erythema, bullae
Skin pain
Mucosal membranes ≥ 2

Causes: Drugs
Stevens-Johnson Syndrome / Toxic epidermal necrolysis

Toxic Epidermal Necrolysis

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, but don’t overhydrate
  - Monitor fluid and electrolyte status
  - Nutritional support
  - Warm environment
  - Respiratory care
- Death (up to 25% of patients with more than 30% skin loss, age dependent)

Stop all unnecessary medications

Ophthalmology consult

Check for Mycoplasma - 25% of SJS in pediatric patients

Treat like a burn patient, but don’t overhydrate

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
  - SJS: high dose corticosteroids -1.5-2 mg/kg prednisone (no RCT)
  - TEN: IVIG 0.5-1g/kg/d x 4d

Case

- 83 yo female admitted for slowly increasing LE erythema and poor response to outpatient antibiotics
- HPI: increasing LE erythema, edema over 3 weeks, somewhat painful
- PMHx: Sjogren’s syndrome, Hashimoto’s thyroiditis, Addison’s disease
The red leg

Infectious
- Cellulitis/erysipelas
- Necrotizing fasciitis
- Pyomyositis

Non-Infectious
- Vasculitis
- Pigmented purpuric dermatosis
- Asteatotic dermatitis
- Pretibial myxedema
- Erythema nodosum
- Contact dermatitis
- Stasis dermatitis

Cellulitis
- Infection of the dermis
- Gp A beta hemolytic strep and Staph aureus
- Rapidly spreading
- Erythematous, tender plaque, not fluctuant
- Lower leg
- Rarely bilateral
- Patient often toxic
- WBC, LAD, streaking
- Treat tinea pedis
Vasculitis
- “Palpable purpura”
- Degree increases from cephalad to caudad
- Favors dependent areas (lower legs)
- May itch, sting, or burn
- Associated sx: fever, malaise, arthralgias
- Characteristic skin biopsy
- Broad differential- consult dermatology

Leukocytoclastic Vasculitis - Etiology
- Conditions associated with LCV
  - Idiopathic (45-55%)
  - Infection (15-20%)
  - Inflammatory diseases (15-20%)
  - Medications (10-15%)
  - Malignancy (<5%)
  - Other
    - Hypergammaglobulinemic purpura of Waldenström
    - HIV
    - Cocaine use (p-ANCA +)
Leukocytoclastic Vasculitis - Etiology
- Infection
  - Group A β-hemolytic Streptococcus
  - Tuberculosis
- Inflammatory diseases
  - Connective tissue disease, inflammatory bowel disease, bowel-associated dermatitis-arthritis syndrome, neutrophilic dermatoses
- Medications
  - sulfonamides, penicillins, allopurinol, phenytoin, thiazides, quinolones…
  - Eosinophils in drug induced vasculitis: 79% systemic, 22% skin only
- Malignancy
  - Lymphoproliferative (>solid)

Pigmented Purpuric Eruption
- 1-3 cm patch/plaques on the lower leg
  - Confluent tiny papules with hemorrhage
  - Brown-yellow hyperpigmentation due to iron deposition
  - Location: Pretibial
  - Natural history: Chronic
  - Elderly males favored
  - Asymptomatic or pruritic

Asteatotic Dermatitis
- Occurs on the lower legs, the flanks, and the arms
- Spares the armpits, groin, face
- First stage: flaking of the skin, pruritic
- Second stage: cracking of the skin looking like the bed of a dry lake; itchy and stings
- Third stage: Weepy dermatitis, ITCHY
- Treatment
  - Moisturize
  - Mid potency topical steroid (TAC) ointment

Pretibial Myxedema
- Bilateral, localized
- Nonpitting infiltration
- Nodules and plaques
- Elephantiasis-like
Thyroid Dermopathy
Pretibial Myxedema
- Treatment
  - Does not respond to treatment of thyroid disease
  - Intralesional triamcinolone
  - High potency topical steroids under occlusion
  - Compression

Erythema Nodosum
- Reactive condition on the lower legs
- Females: Males = 3-10:1
- Tender, deep, red nodules on the anterior-posterior calves; 1-5 cm
- Lesions resolve with faint bruise; do not drain!
- May be associated arthritis/tenosynovitis (ankles, knees); fever
Triggers of EN
- Infections: Strep pharyngitis, tuberculosis, systemic fungus (coccidioidomycosis), Yersinia (diarrhea)
- Sarcoidosis; Behcet’s
- Inflammatory Bowel Disease
- Pregnancy
- Medications: OCP’s

Erythema Nodosum Diagnosis and Treatment
- Clinical, but biopsy if not responding
- Treatment:
  - Elevation, bedrest, reduced exercise
  - Support stockings
  - NSAID’s or indomethacin
  - SSKI 5-15 gtts TID (this works!!)
- Look for the trigger

Contact Dermatitis
- Itch >>> pain
- Patient is non-toxic
- Erythema and edema can be severe
- Topical meds and Rhus dermatitis (Poison Oak) are common causes
- Treat with topical steroids for most cases, but systemic steroids for Rhus dermatitis (2-3 weeks)

Contact Dermatitis
- Leg ulcers are commonly complicated by allergic contact dermatitis
- Common causes
  - Applied antibiotics (Neomycin, Bacitracin)
  - Topical anesthetics (benzocaine)
  - Other (Vitamin E, topical benadryl)
- Avoid all topical antibiotics to leg ulcers (except topical metronidazole to prevent odor)
Stasis Dermatitis/Venous Insufficiency
- Due to venous hypertension
- Often bilateral
- Itchy and/or painful
- Red, hot, swollen leg
- No fever, elevated WBC, LAD, streaking
- Look for: varicosities, edema, venous ulceration, hemosiderin deposition
  - Pinpoint yellow-brown macules and papules = hemosiderin
- Superimposed contact dermatitis common

End stage is permanent sclerosis (sclerotic panniculitis / lipodermatosclerosis) with “inverted champagne bottle” legs

Treat with topical corticosteroids, leg elevation, and compression stockings

Stasis Dermatitis/ Venous Insufficiency and Lymphatic Insufficiency
- As complication of recurrent infection and obesity, edema becomes firm (non-pitting)
- Skin becomes pebbly, hyperkeratotic and rough (elephantiasis verrucosa nostra = lymphostasis verrucosa cutis)
- Ulceration in this setting (with lymphatic and venous insufficiency) is significantly harder to heal
The Red Leg: Key features of the physical exam:

<table>
<thead>
<tr>
<th></th>
<th>Fever</th>
<th>Pain</th>
<th>Warmth</th>
<th>Bilateral</th>
<th>Streaking</th>
<th>Lymphadenopathy</th>
<th>Elevated WBC</th>
</tr>
</thead>
<tbody>
<tr>
<td>Cellulitis</td>
<td>Yes</td>
<td>Yes</td>
<td>Yes</td>
<td>Almost never</td>
<td>Yes</td>
<td>Yes</td>
<td>Yes</td>
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<tr>
<td>Consider another diagnosis</td>
<td>No</td>
<td>+/-</td>
<td>+/-</td>
<td>often</td>
<td>No</td>
<td>No</td>
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Case

- 67M underwent an elective saphenous vein phlebectomy for asymptomatic varicosities
- 4d post op, he develops erythema around the wound.
- Ulceration continues to expand despite multiple debridements and broad spectrum antibiotics.
- Wound cultures are negative
- 3 weeks later, he is transferred to UCSF and a dermatology consultation is called
- Tmax 104, WBC 22
Pyoderma Gangrenosum

- Rapidly progressive (days) ulcerative process
- Begins as a small pustule which breaks down forming an ulcer
- Undermined violaceous border
- Expands by small peripheral satellite ulcerations which merge with the central larger ulcer
- Occur anywhere on body
- Triggered by trauma (pathergy) (surgical debridement, attempts to graft)
Pyoderma Gangrenosum

- 50% have no underlying cause
- Associations (50%):
  - Inflammatory bowel disease (1.5%-5% of IBD patients get PG)
  - Rheumatoid arthritis
  - Seronegative arthritis
  - Hematologic abnormalities (AML)

Pyoderma Gangrenosum

- Workup
  - Skin biopsy for H&E and culture
  - Rheumatoid factor
  - SPEP/UPEP
  - ANCA (ulcers of Wegener granulomatosis can mimic PG)
  - Colonoscopy (r/o IBD)
  - Peripheral smear, Bone marrow biopsy (r/o AML)

Pyoderma Gangrenosum Treatment

- AVOID DEBRIDEMENT
- Refer to dermatology
- Treatment of underlying disease may not help PG
  - Topical therapy:
    - Superpotent steroids
    - Topical tacrolimus
  - Systemic therapy:
    - Systemic steroids
    - Cyclosporine or Tacrolimus
    - Cellcept
    - Thalidomide
    - TNF-blockers (Remicade)
A few simple rules to live by:

- Don’t use lotrisone!
- Never give systemic steroids for psoriasis or atopic dermatitis
- Only 50% of abnormal nails are due to fungal infections
- Do an excisional biopsy to diagnose melanoma
- Cellulitis is almost never bilateral
- Drug eruptions are usually due to medications started 7-10 prior to onset of the rash