Skin Block

• Introduction To Diseases Of The Skin
• Acneiform, Alopecias, and Pigmentary Disorders
• Eczemas, Papulosquamous, and Vesiculobullous Skin Disease
• Skin Neoplasms

• **Drug Eruptions**
• Skin Signs of Systemic Disease
Drug Eruptions

Bernice Kwong, MD
Director, Inpatient Dermatology Consult Service
Director, Supportive Dermato-Oncology Program
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Learning Objectives

At the end of the session, the students will be able to:

• Recognize the most common cutaneous drug reaction patterns encountered in the hospital, including morbilliform eruption, fixed drug eruption, urticarial, drug-induced photosensitivity.

• List and identify warning signs that are suggestive for potentially life-threatening drug eruptions such as DIHS and SJS/TEN
Adverse Cutaneous Drug Eruption

• Any unintended or undesired skin effect of a drug following use for prevention, diagnosis or treatment
• Most common adverse event in hospitalized patients (2-3% of all inpatients)
Adverse Cutaneous Drug Eruptions

• May be immunologic (allergic) or non-immunologic
• most are self-limited
• If eruption is mild and drug is critical, may treat through
• Some reactions (complex drug eruptions) may have systemic manifestations
There are more than 80 specific cutaneous drug reaction patterns seen in the skin ...

- Exanthematous (Morbilliform) drug eruption
- Urticarial
- Erythema Multiforme
- Fixed drug eruption
- Drug-induced photosensitivity
- Drug-induced pigmentation
- Bullous drug eruption
- Lichenoid drug eruption
- Drug-induced vasculitis (palpable purpura)
- Drug-induced non-palpable purpura
- Drug-induced erythroderma
- Stevens Johnson Syndrome
- Toxic Epidermal Necrolysis
- Drug-Induced Hypersensitivity Syndrome
- More ...
Approach to the Initial Assessment of Patient with Suspected Drug Eruption

- **Exclude alternative causes** (viral exanthems, GVHD, infection)
- **Determine type of drug eruption pattern** if possible
- **Look for warning signs** to help differentiate non-life threatening from life-threatening (systemic manifestations)
- **Determine possible culprits**
  - **names** of all medicines (Include over the counter medications)
  - **start date** of all medications
  - **Timing** of symptoms
  - Patient history (has this occurred in past?)
- **Familiarize previous experience of drug events in general population** (frequency, most common timeline for reaction pattern, L.I.T.T.’s dermatology database)
Warning signs

• Fever
• facial edema
• Lymphadenopathy
• swelling of tongue, eyes, lips
• skin pain, blistering, purple color, +Nikolsky sign
• palpable purpura
• SOB, N/V, hypotension, voice change
• mucosal involvement (ocular, oral, genital)
• laboratory abnormalities: eosinophilia, transaminitis, elevated creatinine, atypical lymphocytes
Exanthematosus (morbilliform) Drug Eruption

- Symmetric, blanching, coalescing erythematous macules and papules
- Centrifugal spread (arises on trunk, spreads to proximal extremities)
Exanthematous (morbilliform) Drug Eruption

- Most common medication-induced eruption
  - 75% of all drug eruptions
- Timing: typically 7-14 days after 1st exposure
  - Faster onset with rechallenge (1-3 days)
  - May persist for 1-2 weeks after medication withdrawn
  - May fade with drug continuation
- Ddx: viral exanthem, graft-versus-host disease (GVHD)
- Most common culprits: antibiotics (penicillins, sulfas), NSAIDs, antihypertensives, barbiturates, phenytoin, allopurinol, ...
Urticaria (Hives)
Urticaria (Hives)

- Well-defined blanchable, pink, edematous plaques with pale canter
- Individual lesions last <24 hours
- +/- pruritus
Urticaria (Hives)

- Pathogenesis
  - caused by release of histamine or other vasoactive substances from mast cells
- 9% associated with drugs
- Timing
  - 1-2 weeks after 1st exposure, faster on re-challenge
- Mechanism
  - type I hypersensitivity, IgE mostly
- most common culprits
  - NSAIDs, aspirin, opioids, antibiotics (penicillins and sulfas), blood transfusion/products, CT contrast, ACE inhibitors, diuretics
Urticaria (Hives): warning signs

**Angioedema**
- subcutaneous involvement (swelling of face, GI tract, skin)
- Angioedema may herald anaphylaxis

**Anaphylaxis**
- laryngeal edema, N/V, hypotension, shock
Angioedema

- variant of urticaria, with edema occurring at a deeper level (dermis/Subcutaneous fat)
  - diffuse erythematous swelling of eyelids, lips, tongue, genitalia.
  - malaise, fever, arthralgias, respiratory symptoms, fatigue, abdominal pain, diarrhea
  - Impending anaphylaxis if have hypotension and shock

- can be caused by medications, foods, or idiopathic

CAUTION: Angioedema of the larynx, upper airway, or tongue (of any mechanism) can progress to airway obstruction and asphyxiations

***immediate treatment with epinephrine
Erythema Mutiforme

• Symmetrically distributed erythematous papules and **targetoid** plaques on acral distribution (palms, soles, dorsal and extensor hands/arms/legs/feet) and face

• **Classic Target Lesion**: 3 distinct circular color zones
Erythema Multiforme

- Relatively benign, acute, **self-limited** skin reaction with few complications
- Usually *not* drug related trigger (typically infectious)
  - HSV (most common, ~50%), mycoplasma, salmonella, histoplasma, ...
- Does *not* progress to SJS/TEN
Erythema Multiforme

• +/- limited mucous membrane involvement
• often crusting on lips 2/2 HSV
Fixed Drug Eruption

- Solitary well-demarcated red or red-brown patch
- Skin lesion occurs in the *same exact location* with every exposure to drug
- Usually asymptomatic, sometimes pruritus
Fixed Drug Eruption

• Benign course. Self resolve but tend to leave behind hyperpigmentation
• Recurrent same location each exposure
• Timing: minutes to hours after drug ingestion
• Common culprits: sulfonamides, naproxen, ibuprofen, tetracyclines
Drug-Induced Photosensitivity Reactions
Drug-Induced Photosensitivity Reactions

• Drug-induced Phototoxicity
  – Sunburn-like eruption
  – Non-allergic
  – Burning > pruritus

• Drug-induced Photoallergy
  – Allergic
  – Does not occur in all patients
  – Pruritus > burning
Drug-Induced Phototoxic Reaction

• Pathogenesis: systemic drug in blood vessels absorbs ultraviolet light leading to sunburn. Dose dependent and UV exposure dependent
  – Usually UVA mediated

• Photo-distributed (face, V of chest, dorsal hands/extensor arms; sparing under neck/chin—sharp cutoff at shirt line) bright red, confluent edematous patches and plaques, may have blistering

• Culprits: NSAIDs, quinolones, tetracyclines, voriconazole, vemurafenib, diuretics, quinolones, St. John’s wort
Drug-induced Photoallergic Reaction

- Morphology: erythematous papules, and plaques, initially in photo-distribution, but eventually may spread to outside of photo-protected area
- Culprits: sunscreen, NSAIDs, griseofulvin, antimalarials, quinolones, sulfonamides
Drug-Induced Hypersensitivity Syndrome (DIHS)

- Potentially **life-threatening** drug reaction
- Previously DRESS syndrome (Drug Reaction with Eosinophilic and Systemic Symptoms), however >30% patients without eosinophilia so this name is misleading
- DIHS is now preferred terminology
Drug-Induced Hypersensitivity Syndrome (DIHS)

- Fever
- Marked facial edema
- Tender lymphadenopathy
- Morbilliform, edematous, sometimes pustular eruption, oftentimes with *follicular accentuation* on face, extremities, upper trunk
  - can see vesicles, urticaria, bullae, erythroderma, purpura
Drug Induced Hypersensitivity Syndrome

• timing is typically 2-6 weeks or longer (late onset) after initiation of drug
  • aromatic anticonvulsants (carbamazapene, phenytoin, phenobarbital)
    • 70%-80% cross-reactivity between aromatic anticonvulsants
  • allopurinol
  • sulfonamides
  • minocycline, dapsone, HIV meds (nevirapine, abacavir) …

• pathogenesis: possible relation to human herpesvirus (HHV)-6 reactivation
DIHS: evaluation

If suspicious cutaneous eruption (fever, facial edema, lymphadenopathy, follicular based morbilliform eruption), must investigate for:

1) HEMATOLOGIC ABNORMALITY
   - eosinophilia >1.5
   - atypical lymphocytes

2) INTERNAL ORGAN INVOLVEMENT (may be asymptomatic, may occur months after onset)
   - hepatitis (transaminases)
   - interstitial nephritis (BUN/creatinine)
   - interstitial pneumonia (CXR)
   - myocarditis (recent suggestions for baseline EKG, ECHO, cardiac enzymes)
   - thyroiditis (TSH, repeat in 2 months)
   - encephalitis/aseptic meningitis
   - colitis/esophagitis
   - autoimmune diabetes

*Two important characteristics: multiple organ involvement and eosinophilia*
DIHS: management

Must recognize quickly, systemic steroids and withdrawal of medication critical

• Systemic steroids
  • if severe or multiorgan involvement with prominent systemic symptoms (after exclusion of infection)
  • slow taper over weeks/months
• N-acetylcysteine
  • if liver involved

High rate of rebound/flare with taper as symptoms can last long after discontinuation of medications
Stevens Johnson Syndrome/Toxic Epidermal Necrolysis (SJS/TEN)
Stevens Johnson Syndrome/Toxic Epidermal Necrolysis (SJS/TEN)

- SJS/TEN are the same disease on a spectrum
- Categorized by % total body surface area involved with epidermal detachment:
  - SJS: <10% BSA. 1-5% mortality
  - SJS/TEN overlap: 10-30% BSA
  - TEN: >30% BSA. 25-35% mortality
- Rare but potential life-threatening drug eruption
- Rapid progression is possible
SJS/TEN: Clinical

- timing: 1-3 weeks after drug ingestion
- prodrome (days): fever, malaise, headache, vomiting, diarrhea, cough, coryza, pharyngitis, myalgias, arthralgias
- starts abruptly
- hallmark: mucocutaneous tenderness and erythema and extensive exfoliation
  - lips and mouth 100%
  - eyes 91%
  - Nose
  - Genital
  - anal mucous membranes
- +Nikolsky
- Morphology: dusky red macules on trunk and extremities, irregular, Erosion and ulcerations of skin, bullae.
Stevens Johnson Syndrome/Toxic Epidermal Necrolysis (SJS/TEN)

• Pathogenesis:
  – Almost always drug induced
  – Host inability to detoxify drug metabolite, leading to cell-mediated cytotoxic T cell response, apoptosis of keratinocytes

• Common culprits: NSAIDs, antibiotics, anticonvulsants
Stevens Johnson Syndrome/Toxic Epidermal Necrolysis (SJS/TEN)

Risk factors

- Age >40
- HR >120bpm
- Malignancy history
- BSA >10%
- BUN > 10
- Bicarbonate, serum <20
- Blood glucose >252
Stevens Johnson Syndrome/Toxic Epidermal Necrolysis (SJS/TEN)

Risk factors
- Age >40
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**SCORTEN** mortality calculation based on score from above criteria
- **0-1**: 3.2% mortality
- **2**: 12.1%
- **3**: 35.3%
- **4**: 58.3%
- **5**: 90%
SJS/TEN: systemic complications

- pulmonary involvement (pneumonitis 23%, bronchitis 6%)
- tracheal ulceration
- restrictive lung disease
- esophageal ulceration
- renal involvement
- nephritis, renal failure
- Dehydration
- electrolyte disturbances
- temperature dysregulation
- scarring from infection
- Pyoderma
- sepsis
SJS/TEN: initial management

- Must rapidly withdraw offending drug, ICU/burn unit for skin care to prevent mortality for sepsis (silver dressings, etc), ophthalmology, electrolyte management, etc.
Chemotherapy related skin side effects

• Non-allergic cutaneous adverse effects due to cancer therapy

• Knowledge and early/consistent management of the most common skin side effects of cancer therapies is critical
  – Improve patient quality of life
    • even one less day, or one hour of less pain or itching is significant
    • Psychosocial impact
  – Prevent unnecessary dose reduction or discontinuation of cancer therapy
21F with metastatic EGFR mutated small bowel adenocarcinoma recently started panitumumab (EGFR inhibitor)

Epidermal Growth Factor Receptor (EGFR) inhibitor related papulopustular (acneiform) eruption
EGFR inhibitor-associated papulopustular eruption

- most common cutaneous complication of EGFR-inhibitors
  - gefitinib (44%)
  - erlotinib (49-75%)
  - cetuximab, panitumumab (up to 90%)
- erythematous papules, pustules on face, chest, back beginning 1-2 weeks after treatment initiation
- not life threatening; not a contraindication to continued therapy positive correlation between rash severity and antitumor activity (patients with advanced non-small cell lung cancer receiving erlotinib)
  - grade 0 rash: 1.5 month median survival
  - grade 1 rash: 8.5 month median survival
  - grade 2-3 rash: 19.6 month median survival
- reduction in patient quality of life (cosmesis, pruritus) leads to dose reduction/discontinuation of chemotherapy
**EGFR**

- tyrosine kinase receptor
- important target in treatment of epithelial cancers (lung, colon, glioblastoma multiforme, papillary thyroid, squamous cell carcinoma)

- in skin, expressed in
  - basal keratinocytes
  - hair follicles
  - sweat glands

- EGFR inhibition
  - growth arrest, apoptosis, premature differentiation of basal keratinocytes
  - inflammatory cell recruitment

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**MONOCLONAL ANTIBODIES TO EGFR**

<table>
<thead>
<tr>
<th>MONOCLONAL ANTIBODIES TO EGFR</th>
<th>SMALL MOLECULE TYROSINE KINASE INHIBITORS</th>
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<tbody>
<tr>
<td>Cetuximab (Erbitux)</td>
<td>Gefitinib (Iressa)</td>
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<tr>
<td>Panitumumab (Vectibix)</td>
<td>Erlotinib (Tarceva)</td>
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<tr>
<td>Trastuzumab (Herceptin), Pertuzumab (Perjeta)</td>
<td>Lapatinib (Tykerb), Afatinib</td>
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72 hours later, no dose reduction
65F with metastatic BRAF mutated thyroid cancer receiving vemurafenib (BRAF inhibitor)
BRAF inhibitor-related skin eruptions

- Keratosis pilaris like eruption
- Invasive squamous cell carcinoma
- Radiation recall
- Eruptive nevi
- Painful eruptive milia
- Hyperkeratosis of the soles
BRAF inhibitor-related eruptive cutaneous SCCs and KAs

Median time to presentation ~8 wks
- 4–31% (vemurafenib)
- 6–11% (dabrafenib)
48F with metastatic neuroendocrine tumor of the pancreas receiving sorafenib

Chemotherapy induced radiation recall
Chemotherapy-related Radiation Recall

- acute and localized inflammatory reaction in previously irradiated skin after exposure to sorafenib
- may occur with many agents (Doxorubicin, daunorubicin, taxanes, actinomycin D, capecitabine, gemcitabine, vemurafenib...)

[Image of skin with radiation recall reaction]
Hand-Foot Syndrome

- **non-allergic**, toxic reactions
- Painful erythema, edema, sometimes bullae often involves the hands and feet
- occurs within the first week of treatment.
- Common provoking agents include: cytarabine (cytosine arabinoside), 5-fluorouracil, doxorubicin, hydroxyurea, and mercaptopurine.
Pathogenesis: unclear

• Toxic insult to cells of the eccrine duct, acrosyringium, and epidermis

• Eccrine sweat secretion of chemotherapeutic agents → preferential concentration at certain sites
  – Palms and soles (high density of eccrine glands)
  – Intertriginous areas (increased sweating/occlusion)
Natural evolution of toxic erythema of chemotherapy
Take Home Points

• Exanthematous or morbilliform drug eruption is the most common type of adverse cutaneous drug reaction and usually arises 7-14 days after initiation of the medication.

• Erythema multiforme is a relatively benign, acute, self-limited skin reaction with few complications, typically triggered by infections such as HSV or mycoplasma, rather than drug. The classic clinical feature is the target lesion.

• Drug-induced photosensitivity reactions can be categorized into phototoxic reaction, which cause more burning and confluent erythema and pain, and the photoallergic reactions which are much more pruritic than burning. Phototoxic reactions are usually mediated by UVA light, which is not filtered by car window-glass.
Take Home Points

• Drug-induced hypersensitivity Syndrome is a severe, potentially life-threatening allergic reaction to medication characterized by classic fever, facial edema, lymphadenopathy, transaminitis and elevated serum creatinine. The reaction usually arises 1-8 weeks after initiation of medication (delayed)

• Stevens Johnson Syndrome/Toxic Epidermal Necrolysis is a rare but possibly life-threatening adverse drug eruption. Mucosal involvement is common.