NOT JUST A RASH:
SERIOUS AND LIFE-THREATENING
DERMATOLOGIC CONDITIONS

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CONFLICT OF INTEREST STATEMENT

Amgen shareholder: Amgen manufactures Enbrel (etanercept), a TNF-inhibitor. There are reports of off-label use of TNF inhibitors to treat TEN and pyoderma gangrenosum.

I have no other relevant conflicts of interest.
OBJECTIVES

• Identify the most common serious and life-threatening dermatologic conditions in adults and children:

• Recognize features and clinical presentations of serious conditions to help distinguish from more benign disorders

• Identify drugs most often associated with serious reactions

• Formulate plans for immediate management of life-threatening dermatoses
SERIOUS OR LIFE-THREATENING DERMATOSES

- Drug reactions – SCAR (Severe Cutaneous Adverse Reactions)
- Infections
- Other disorders
SCAR: SERIOUS CUTANEOUS DRUG REACTIONS

- Erythema multiforme spectrum:
  - EM Major (EMM)
  - Stevens Johnson Syndrome (SJS)
  - Toxic Epidermal Necrolysis (TEN)

- Drug Reaction with Eosinophilia and Systemic Symptoms (DRESS)

- Acute Generalized Exanthematous Pustulosis (AGEP)
INFECTION ASSOCIATED SERIOUS DERMATOSES

- Staphylococcal scalded skin
- Herpes simplex
  - infants and immunocompromised
  - Associated with eczema – eczema herpeticum
- Disseminated cutaneous candidiasis in infants
OTHER SERIOUS CONDITIONS

• Pyoderma Gangrenosum

• Calciphylaxis
ERYTHEMA MULTIFORME SPECTRUM

- Erythema multiforme major
  - Targetoid, raised skin lesions plus 2 mucosal areas eroded
  - Skin detachment <10% BSA
- Stevens-Johnson Syndrome
  - Erythematous flat lesions
  - Skin detachment <10% BSA
- SJS-TEN overlap
  - Flat erythema
  - Skin detachment 10-30% BSA
- Toxic epidermal necrolysis
  - Flat generalized erythema
  - Skin detachment >30% BSA
ERYTHEMA MULTIFORME MAJOR

- Hypersensitivity reaction to drugs and infectious agents
- Causative agent identified only half the time – drugs most common cause
- HSV associated EM often recurs
- Most common Infectious causes
  - Herpes simplex I
  - Herpes simplex II
  - Mycoplasma
  - Epstein Barr Virus
  - Hepatitis viruses
  - Cytomegalovirus
DRUGS CAUSING EMM-SJS-TEN

- Trimethoprim-sulfamethoxazole is most common drug cause
  - 30% due to sulfa drugs/sulfonamides especially in slow acetylators
- Anticonvulsants: barbiturates phenytoin, hydantoin, valproic acid, lamotrigine
- Antibiotics: penicillins, cephalosporins, ciprofloxacin, tetracyclines, erythromycin, vancomycin
- Allopurinol
- Analgesics and antipyretics: aspirin, phenylbutazone, oxyphenbutazone, NSAIDS
- Rifampin, isoniazid and other anti-tuberculin drugs
- Oral contraceptives, quinine, clofibrate, cimetidine, corticosteroids, hydralazine, fluconazole, gabapentin, methotrexate, minoxidil, nystatin, nifedipine, antiretrovirals, verapamil, vaccines, and more
EMM CLINICAL PRESENTATION

• Flulike prodrome of fever, cough, myalgias, sore throat beginning a few days – 2 weeks before rash appears

• Begins as reddish macules, papules or urticarial lesions that expand in concentric rings or arcuate. Center dull red, rings are pink to red; may blister; center turns grey, lesions blister

• Lesions evolve over 72 hrs, well demarcated

• Target lesions on palms of hands very common

• Mild itching in some patients

• Acral areas first affected, symmetric, spreads to torso, neck and face

• Mucosal ulceration in 70% patients: oropharyngeal, conjunctivae, genital areas; can also involve GI, GU and pulmonary mucosal surfaces

• Hemorrhagic bullae and crusts especially in mucocutaneous areas
SJS – TEN

• Complex hypersensitivity reaction process involving cytotoxic T cells and Fas-Fas ligand induced keratinocyte apoptosis

• Genetic component
  • Carbamazapine and allopurinol induced SJS/TEN associated with HLA-B*1502 allele

• Clinical presentation – similar prodrome and skin lesions
• May start as EM rash, diffuse patchy erythema, or generalized erythema
• First lesions may be mucosal
• **Painful skin is characteristic feature**
<table>
<thead>
<tr>
<th>SJS</th>
<th>SJS-TEN Overlap</th>
<th>TEN</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Primary lesions</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Erythematous to dusky macules</td>
<td>Erythematous to dusky macules</td>
<td>Erythematous to dusky macules, poorly delineated red plaques</td>
</tr>
<tr>
<td>Flat atypical targets</td>
<td>Flat atypical targets</td>
<td>Flat atypical targets</td>
</tr>
<tr>
<td>Bullae, erosions, necrosis</td>
<td>Bullae, erosions, necrosis</td>
<td>Bullae, erosions, necrosis</td>
</tr>
<tr>
<td>Confluent on face and trunk</td>
<td>Greater confluence on face and trunk</td>
<td>Greatest confluence on face, trunk, and elsewhere</td>
</tr>
<tr>
<td><strong>Mucosal involvement</strong></td>
<td>Yes</td>
<td>Yes</td>
</tr>
<tr>
<td><strong>Systemic symptoms</strong></td>
<td>Usually</td>
<td>Always</td>
</tr>
<tr>
<td><strong>Epidermal detachment (% body surface area)</strong></td>
<td>&lt;10%</td>
<td>10–30%</td>
</tr>
</tbody>
</table>

*From Dermatol Ther, 2011; 207-218*
### SCORTEN CRITERIA

<table>
<thead>
<tr>
<th>Condition</th>
<th>Score</th>
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</thead>
<tbody>
<tr>
<td>Serum blood urea nitrogen &gt;10 (mmol/L)?</td>
<td>1 point</td>
</tr>
<tr>
<td>Serum bicarbonate &lt;20 (mmol/L)?</td>
<td>1 point</td>
</tr>
<tr>
<td>Serum glucose &gt;14 (mmol/L)?</td>
<td>1 point</td>
</tr>
<tr>
<td>Age &gt;40 years?</td>
<td>1 point</td>
</tr>
<tr>
<td>Malignancy present?</td>
<td>1 point</td>
</tr>
<tr>
<td>Heart rate &gt;120?</td>
<td>1 point</td>
</tr>
<tr>
<td>Percentage body surface area &gt;10%?</td>
<td>1 point</td>
</tr>
</tbody>
</table>

*From Dermatol Ther, 2011; 207-218*
# SCORTEN MORTALITY

<table>
<thead>
<tr>
<th>Total score</th>
<th>Mortality (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>1 SCORTEN, Score of toxic epidermal necrolysis.</td>
<td></td>
</tr>
<tr>
<td>0–1 points</td>
<td>3.2</td>
</tr>
<tr>
<td>2 points</td>
<td>12.2</td>
</tr>
<tr>
<td>3 points</td>
<td>35.3</td>
</tr>
<tr>
<td>4 points</td>
<td>58.3</td>
</tr>
<tr>
<td>5 or more points</td>
<td>90</td>
</tr>
</tbody>
</table>

*From Dermatol Ther, 2011; 207-218*
EMERGENCY MANAGEMENT

• Recognize SJS-TEN
• Discontinue offending drugs
• Airway management
• hydration and hemodynamic support 4-6 L fluid/day in first few days in TEN
• Skin – wound care
  • Hospitalize patients with >10% BSA in burn unit if available
• Ophthalmology consultation
• SCORTEN assessment - Laboratory studies
• Consider pharmacologic and other therapies
• Antibiotics, antiviral therapy when appropriate
• Pain management

• Crit Care Med 2011, 39:1521
PHARMACOLOGIC TREATMENTS
SHOULD CORTICOSTEROIDS BE USED?

- EMM: 0.5-1mg/kg/day prednisone
- SJS: no studies since 1994 have shown increased mortality with steroid use
  - Most studies used methylprednisolone dose range 160-1000mg/day or dexamethasone 1.5mg/kg per day
  - Pulse or limited treatment to 5 days or less
- TEN: corticosteroid use controversial
  - Pulse methylprednisolone for 1-2 days
  - 64 patients assessed 2001-2011: patients treated with IVIg had higher mortality than those treated with cyclosporine 3-5mg/kg/day (standardized mortality ratio: 1.43, 0.43)
  - Anecdotal reports and small studies: plasmapheresis, TNF-inhibitors infliximab and etanercept, GCSF

J Am Acad Dermatol 2014; 941
J Am Acad Dermatol 2013; 187
Dermatol Ther 2011; 207
DRESS: DRUG REACTION WITH EOSINOPHILIA AND SYSTEMIC SYMPTOMS

- Formerly known as drug hypersensitivity syndrome or anticonvulsant hypersensitivity syndrome
- Triad of rash, fever and systemic organ involvement
  - 100% hematologic, 80% hepatic, 40% renal, 33% pulmonary
    - Hematologic: eosinophilia, lymphocytosis, atypical lymphs, thrombocytopenia, neutropenia, agranulocytosis
    - Multi-organ involvement: lymphadenopathy, hepatitis, hepatic necrosis, interstitial nephritis, renal failure, pneumonitis, rhabdomyolysis, myopathy
- Occurs 1/1000 – 1/10000 drug exposures, most due to anticonvulsants
- Reaction thought to be due to genetically determined altered ability to detoxify intermediate drug metabolites; Asians most affected
- 10% mortality rate

*J Am Acad Dermatol 2013, vol 5*
DRESS

- Begins 2-8 weeks after starting medication
- Anticonvulsant drugs most common cause: phenytoin, carbamazepine, lamotrigine, phenobarbital
  - Cross reactivity between aromatic anticonvulsants
- Other drugs implicated: minocycline, allopurinal, dapsone, sulfamethoxazole-trimethoprim, terbinafine, omeprazole, amiodarone, piperacillin, amoxicillin, ciprofloxacin, captopril, azothiaprine, nevirapine, abacavir, sulfasalazine
  - Dapsone can induces within a few days
- Biologics: vemurafenib, infliximab
- If re-exposed to drug, reaction will occur within hours to few days
CLAIRICAL

- Presents first with fever then rash
- Typical is morbilliform eruption beginning on face and extremities then rapidly spreads and may cover most of the body
  - Facial edema common
  - Erythroderma with diffuse eruptions
  - Blistering and mucosal sores can occur
- Tender lymphadenopathy begins with cervical nodes then generalized adenopathy
- Pharyngitis within a few days of fever onset
- High temps are characteristic
- Transaminitis often first evidence of systemic organ involvement
- Severe reactions have high rate of multiorgan damage and mortality: hepatic necrosis, renal failure, pneumonia, rhabdomyolysis, cardiomyopathy, pancreatitis
DIAGNOSIS

- Characteristic triad: rash, fever, organ involvement is diagnostic in setting of drug exposure
- Key factor: rash appear 2-8 weeks after starting offending drug
- Eosinophilia is prominent laboratory finding
- More common in patients previously treated with systemic steroids
- ALT >100 indicative of need for steroid therapy
- Differential: lymphoma, pseudolymphoma, viral exanthem, hypereosinophilic syndrome

CRITICAL: distinguish from SJS – TEN because steroids are life-saving
MANAGEMENT

- Stop offending drug
- Early treatment critical to limit disease progression and reduce mortality
  - Prednisone 0.5-1mg/kg/d
  - Methylprednisolone 1mg/kg/d
  - Concommitant potent topical steroids (clobetasol ointment)
  - Prolonged steroid therapy may be necessary – early discontinuation may be associated with flares
- Viral reactivation may be a factor: HHV-6, EBV, CMV
DRESS CRITERIA

- Acute skin rash
- Involvement of at least one internal organ
- Lymphadenopathy at 2 sites
- One or more hematologic abnormalities:
  - Lymphocytosis or lymphopenia (+/- atypical lymphs)
  - Eosinophilia
  - Thrombocytopenia
- Fever >38°C
- +/- transaminase elevation
AGEP: ACUTE GENERALIZED EXANTHEMATOUS PUSTULOSIS

- AGEP: Hypersensitivity drug reaction characterized by an acute febrile illness with rapidly progressive generalized pustular eruption
- Rash: small non-follicular pustules on red skin with predilection for skin folds (neck, axillae, groin) then spreads to trunk and upper extremities
  - Desquamation as disease resolves
- Facial edema and prickly or slight burning skin sensation
- Temp >38° begins with rash onset
- Leukocytosis, neutrophilia
- Begins within hours of first drug dose
- Spontaneous resolution within 7-10 days
- May be associated with hepatitis, renal failure and hypocalcemia
CAUSES OF AGEP

- Antibiotics: penicillins, macrolides, quinolones
- Carbamazepine
- Diltiazem
- Antimalarials
- SSRI

- Viral infections: parvovirus, EBV, HHV-6 have been implicated
MANAGEMENT

- Stop offending drug
- Topical steroids for most cases
- If severe, widespread disease and/or systemic involvement use systemic corticosteroids
- Methotrexate and etretinate used especially if severe hand-foot involvement will resolve within a few days
STAPHYLOCOCCAL SCALDED SKIN

- Staphylococcal toxin mediated disease most common in infants and young children
- Large areas of patchy red rash or erythroderma (generalized red skin)
- Blisters can appear followed by desquamation
- No mucous membrane involvement
- Fever
- May have febrile prodrome before rash appears
ECZEMA HERPETICUM

- Herpes simplex viral spread in eczematous skin
- Most often seen in children with moderate to severe atopic dermatitis
- Discrete vesicles and pustules within eczematous patches
- Crusting similar to impetigo
- Peri-oral, nasal areas often affected
- Pain replaces typical itching characteristic of eczema
- Fever
- Periorbital involvement requires prompt antiviral therapy
• Can be associated with herpes encephalitis in infants
• Bell’s palsy infrequent complication
• May have concomitant Staph aureus infection
• Several reports of eczema herpeticum triggering Stevens Johnson syndrome in young children

• Treat acutely with acyclovir or valacyclovir
• Atopic dermatitis patients often require HSV suppressive treatment
• Treat coincident Staph infection
• Aggressive atopic derm management to control disease
DISSEMINATED CUTANEOUS CANDIDIASIS

- Generalized pustular eruption in newborns, young infants
- Begins with few miliaria-like pustules often on face and scalp
- Lesions spread over hours to few days
- Associated with fever
- Most often seen with vaginal deliveries
- Requires systemic antifungal therapy
PYODERMA GANGRENOsum

- Immunologically mediated neutrophilic process
- Associated most often with inflammatory bowel disease, rheumatoid arthritis and myeloid disorders
- Can precede onset of systemic disease particularly leukemia
- Begins as painful pustule on bright red base, expands rapidly, ulcerates
- Single or multiple lesions are well-circumscribed
- Violaceous undermined borders with meaty red based, become necrotic
- Expand or worsen with manipulation, trauma
- May have associated fever, lymphadenopathy, neutrophilia
- Most often misdiagnosed as brown recluse spider bites
• High index of suspicion
• Characteristic lesions cue diagnosis
• Dermatology consult may eliminate need for biopsy
  • Histology is not pathognemonic
• Early treatment with cyclosporin or remicade results in rapid resolution
CALCIPHYLAXIS

- Extremely painful necrotic lesions
- Vascular thrombosis causes avascular skin necrosis
- Lower extremities most common site
- Primarily seen in poorly controlled diabetics