Dermatology in the ICU

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I do not have a financial interest/arrangement or affiliation with one or more organizations that could be perceived as a real or apparent conflict of interest in the context of the subject of this presentation.
Presentation Overview

- Brief Overview of Cutaneous Manifestations of Systemic Disease
- Drug Reactions
Cutaneous Manifestations of Systemic Disease

- Frequently encountered in ICU setting
- May be the initial sign of an internal disease
Liver Disease
Jaundice
Gynecomastia
Kaput Medusa
Spider Angiomas
Lichen Planus
Lichen Planus
Lichen Planus
Hemochromatosis
Porphyria Cutanea Tarda
Porphyria Cutanea Tarda
Xanthomas
Xanthomas
Xanthomas
Tendinous Xanthomas
Xanthelasma
Renal Disease
Pruritus
Pruritus

- Optimize Dialysis
- Gentle cleansing of skin (minimal soap)
- Emollients TID
- Topical Steroids BID
  - Triamcinilone 0.1% Ointment
- Menthol Cream
- Systemic Anti-histamines and steroids ineffective
- Narrowband UVB mainstay of outpt therapy
- Transplant
Acquired Perforating Disorder (Kyrle Disease)
Nephrogenic Systemic Fibrosis

Nephrogenic Systemic Fibrosis
Nephrogenic Systemic Fibrosis

- Scleroderma-like disorder that affects both the skin and internal organs
- Renal insufficiency and exposure to gadolinium-based contrast agents
- Patterned, thick, indurated plaques distributed symmetrically on the extremities
  - Erythematous to hyper pigmented plaques with an irregular advancing edge with an “amoeboid” appearance
- Confluent involvement on the extremities often results in joint contractures.
- Treatment is unsatisfactory
  - Steroids and other immunosuppressive
Calciphylaxis
Calciphylaxis
Calciphylaxis
Calciphylaxis

- Progressive vascular calcification as well as ischemic necrosis of the skin and soft tissues
- Early lesions are violaceous reticulated patches
- Bullae or a gray color may develop within the lesions, signifying imminent tissue necrosis and ulcer formation
- Extremely painful even at the earliest stages of development
- Death is often due to gangrene and sepsis
  - Up to 85%
  - Proximal lesions with worst prognosis
Calciphylaxis

- **Treatment:**
  - Normalization of the calcium-phosphate product by low calcium dialysis/PTH levels
  - Phosphate binders
    - Calcium acetate and magnesium carbonate
  - Aggressive wound care
  - Sodium thiosulfate
  - Pamidronate
Pulmonary Disease
Cyanosis
Acquired Nail Clubbing
Nail Clubbing

- Can be congenital or acquired
  - Congenital heart disease/ Cystic Fibrosis
- 80% of acquired associated with pulmonary disease
  - CHF/ IBD/ HIV/ Hyper Thyroid/ Carcinoma/ Cirrhosis
- Enlargement of soft tissue of the distal digit
- Nail plate has greater than 180° widening of the angle between the proximal nail fold and the nail plate
Sarcoidosis
Lupus Pernio
Sarcoidosis
Sarcoidosis
Sarcoidosis
Sarcoidosis
Sarcoidosis

- Systemic granulomatous disease of unknown etiology
- Cutaneous manifestations in up to one-third of patients
  - May be the first clinical sign of the disease
- Red-brown to violaceous papules and plaques appear most often on the face, lips, neck, upper back and extremities
- Classic finding is the development of within pre-existing scars or at sites of prior trauma
Sarcoidosis

- Lung disease occurs in up to 90% of patients
  - Alveolitis to granulomatous infiltration of the alveoli, blood vessels, bronchioles, pleura and fibrous septa
  - End stage of pulmonary sarcoidosis is fibrosis with bronchiolectasis and “honeycombing” of parenchyma
  - Hilar and/or paratracheal lymphadenopathy, usually asymptomatic, 90% of patients
- Ocular disease 25-50%
- Cutaneous disease 10-35%
- Osseous disease 10-15%
- Neurological disease 5-10%
Lofgren’s Syndrome
Erythema Induratum
Erythema Induratum
Cardiovascular Disease
Endocarditis

Janeway lesions

Osler’s Nodes

Endocarditis

Splinter Hemorrhages
Endocarditis

Subconjunctival haemorrhages (2–5%)

Cerebral emboli (15%)

Roth's spots in fundi (rare, < 5%)

Petechial haemorrhages on mucous membranes and fundi (20–30%)

Poor dentition

Splenomegaly (30–40%, long-standing endocarditis only)

Systemic emboli (7%) Nail-fold infarct

Varying' murmurs (90% new or changed murmur)

Conduction disorder (10–20%)

Cardiac failure (40–50%)

Haematuria (60–70%)

Osler's nodes (5%)

Petechial rash (40–50%, may be transient)

Loss of pulses

Digital clubbing (10%, long-standing endocarditis only)

Splinter haemorrhages (10%)
Cholesterol Emboli
Cholesterol Emboli
Endocrine Disorders
Moon Facies
Moon Facies
Buffalo Hump
Striae
Acanthosis Nigricans
Diabetic Dermopathy
Diabetic Dermopathy and Bullae
Insulin Lipodystrophy
Necrobiosis Lipoidica
Necrobiosis Lipoidica
Granuloma Annulare
Granuloma Annulare
Granuloma Annulare
Granuloma Annulare
Graves

Pretibial Myxedema
Graves
Hypothyroidism

Generalized Myxedema
Connective Tissue Disease
Malar Rash
Malar Rash
Discoid Lesions
Discoid Lesions
Dermatomyositis
Dermatomyositis
Dermatomyositis

Gottron’s Papules
Dermatomyositis
Scleroderma
Scleroderma

Sclerodactyly  

Calcinosis
Scleroderma

Sclerodactyly

Calcinosis
Scleroderma
Scleroderma
Morphea
Morphea
Morphea
Drug Reactions
Drug Reactions

- The skin is common target for adverse drug reactions
- Logical approach is needed based on clinical characteristics, chronologic factors and use of a literature search
- Drug reactions can have a polymorphous morphology
  - Urticaria, purpura, full thickness epidermal necrosis, annular patches
  - Exanthematous eruptions and urticaria are the two most common
- Early differentiation between a severe drug eruption vs an uncomplicated drug eruption is critical
  - Dermatological consultation can be useful
Severe Cutaneous Adverse Reactions

- Drug reaction with eosinophilia and systemic symptoms (DRESS)/ drug-induced hypersensitivity syndrome (DIHS)
- Stevens–Johnson syndrome and Toxic epidermal necrolysis
- Bullous drug eruption (Linear IG-A, Pemphigus, Vulgaris, Bullous Pemphigoid)
- Anaphylaxis
- Anti-coagulant induced skin necrosis
- Generalized Fixed Drug
Epidemiology

- 2% of all drug-induced skin reactions are considered “serious”
- 1 in every 1000 hospitalized patients will have a serious drug reaction
- World Health Organization definition:
  - “if it results in death, requires hospitalization or prolongation of existing hospital stay, results in persistent or significant disability/ incapacity, or is life-threatening”
Epidemiology

- Increased age, female gender, and number of drugs
- AIDS (10-50x greater Morbilliform risk to Sulfa)
- Primary responsible drugs penicillins, cephalosporins, sulfonamides, anti-epileptic, and nonsteroidal anti-inflammatory drugs (NSAIDs).
Pathogenesis

- Immune Mediated Drug Eruptions
- Non Immune Mediated
  - (sometimes predictable)
- Idiosyncratic
Pathogenesis

- Immune Mediated Drug Eruptions
  - IgE-dependent drug reactions
  - Cytotoxic drug-induced reactions
  - Immune complex-dependent drug reactions
  - Cell-mediated reactions
Immune Mediated Drug Eruptions

- **IgE-dependent drug reactions** (formerly type I, Gell-Coombs classification):
  - Urticaria, angioedema and anaphylaxis

- **Cytotoxic drug-induced reactions** (antibody against a fixed antigen; formerly type II):
  - Petechiae secondary to drug-induced thrombocytopenia

- **Immune complex-dependent drug reactions** (formerly type III):
  - Vasculitis, serum sickness and certain types of urticaria

- **Possible delayed-type, cell-mediated drug reactions** (formerly type IV; sometimes not well defined):
  - Exanthematous, fixed and lichenoid drug eruptions, Stevens-Johnson syndrome (SJS) and TEN.
Pathogenesis

✓ Non Immune Mediated (sometimes predictable)
  ✓ Overdose, Cumulative Toxicity, Drug-Drug Interaction
  ✓ Exacerbation of Disease (androgen/steroids acne)
  ✓ Delayed (arsenic induced SCC, alkylating agent induced leukemia)
Pathogenesis

✓ Idiosyncratic
  ✓ DRESS
  ✓ SJS/ TEN
  ✓ Drug reactions in HIV
Making the Diagnosis

- Clinical Characteristics
  - Primary lesions
    - Urticarial, erythematous papule, pustule, purpuric papule, vesicle or bulla
  - Distribution and number of lesions
  - Mucous membrane involvement, facial edema
  - Associated signs and symptoms:
    - fever, pruritus, lymph node enlargement, visceral involvement
Making the Diagnosis

- **Chronological Factors**
  - Document all drugs to which the patient has been exposed (including OTC and complementary) and the dates of administration
  - Date of eruption
  - Time interval between drug introduction (or reintroduction) and skin eruption
  - Response to removal of the suspected agent
Morbilliform Drug Eruptions

- Most common drug rash
- Usually begins 7-14 days after beginning medication
- Erythematous maculopapular eruption, + pruritis
- No mucosal involvement
- May have low-grade fever but usually do not appear toxic
- Penicillins, sulfa, cephalosporins, anticonvulsants
- D D x: Viral exanthem, DRESS, SJS/ TEN
Morbilliform Drug Eruptions
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Morbilliform Drug Eruptions

- Treatment is largely supportive
  - Topical antipruritics and corticosteroids may help to alleviate pruritus
- Discontinuing the offending agent is the first therapeutic measure
- “Treating through”, i.e. continuing the drug despite the cutaneous eruption, can be considered when the suspected drug is of paramount importance for the patient and there is no satisfactory
MORBILLIFORM DRUG ERUPTIONS

- Dissappears within a few weeks
  - Few patients may experience a progressive worsening, leading to erythroderma
- Whether continuation of the drug can lead to SJS is debatable
- “Leaving the same station”, they may be on different tracks from the beginning.
Urticaria and Angioedema

- Transient erythematous and edematous papules and plaques
- Pruritic
- Individual lesions last less than 24 hours
- Occurs on re-exposure to causative agent
- <10% urticaria caused by drugs
- Penicillins, cephalosporins, sulfa, tetracyclines, NSAIDs
Urticaria and Angioedema

- Angioedema is transient edema of dermis and subcutaneous tissue
- Ace inhibitors, NSAIDs, Penicillins, Cephalosporins, contrast dyes
Photosensitivity

- Light + Drug = photosensitivity eruption
- Seen on sun-exposed skin
- Erythema +/- pruritus
- Tetracyclines, NSAIDs, fluoroquinolones, sulfa drugs
Photosensitivity
**Acute Generalized Exanthematous Pustulosis (AGEP)**

- Small pustules on edematous, erythematous skin; burning or pruritic
- Starts about 2 days after starting the drug
- **Systemic signs**: High fever, eosinophilia, transient renal dysfunction, normal LFTs
- Beta-lactam antibiotics, macrolide antibiotics most common causes
Drug Reaction with Eosinophilia and Systemic Symptoms (DRESS)/ Hypersensitivity Syndrome

- Morbilliform edematous with follicular accentuation; morphology varies
- 2-6 weeks after beginning offending drug
- **Systemic signs:** Fever, hepatitis, eosinophilia, myocarditis, nephritis, pneumonitis, atypical lymphocytosis, arthritis, lymphadenopathy
- Hepatitis may be fatal
- Anticonvulsants (phenytoin, lamotrigine, carbamazepine), sulfa drugs, allopurinol most common causes
Drug Reaction with Eosinophilia and Systemic Symptoms (DRESS)/ Hypersensitivity Syndrome

- Lymph nodes are often enlarged
- Arthralgias or even arthritis may be seen.
- Most common (and usually the most severe) site of visceral involvement is the liver
  - Sometimes fulminant
  - Responsible for the majority of deaths (10% of cases)
- Myocarditis, interstitial pneumonitis, interstitial nephritis, thyroiditis and even infiltration of the brain by eosinophils may be observed.
- Allopurinol induced gastrointestinal bleeding
- Serial CBC with diff, CMP, initial C-Xray, EKG, and TSH
DRESS
DRESS
DRESS
DRESS
DRESS
Treatment of DRESS

- Early withdrawal of the offending drug is mandatory.
- Corticosteroids represent the first line of therapy.
- Systemic corticosteroids are recommended for life-threatening involvement of the lung and heart because the inflammation is responsive to corticosteroids.
  - Not particularly useful for reversing kidney and/or liver disease.
  - Relapse can occur when the dosage is tapered.
  - Steroid therapy sometimes weeks to months.
  - Serial CBC with Diff, CMP, TSH.
Stevens-Johnson Syndrome (SJS) and Toxic Epidermal Necrolysis (TEN)

- Consider both on a spectrum of disease
- Cell-mediated reaction → apoptosis
- 7-21 days after drug exposure
- Erythematous and purpuric macules and targetoid lesions, leading to flaccid bullae and full thickness epidermal detachment, leaving dermis behind
SJS and TEN

- Palms and soles often involved
- **Systemic signs:** Fever, prodrome with URI-type symptoms, mucosal lesions
- Prone to fluid imbalance, sepsis
- NSAIDs, sulfa, allopurinol, anticonvulsants, penicillins
### Epidemiology

#### STEVENS–JOHNSON SYNDROME (SJS) AND TOXIC EPIDERMAL NECROLYSIS (TEN): EPIDEMIOLOGY AND RISK FACTORS

<table>
<thead>
<tr>
<th>Category</th>
<th>Description</th>
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<tbody>
<tr>
<td>Annual incidence</td>
<td>1.2–6 per million (SJS)</td>
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<tr>
<td></td>
<td>0.4–1.2 per million (TEN)</td>
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<tr>
<td>Ratio women : men</td>
<td>1.5 : 1</td>
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<td>Risk factors</td>
<td>Slow acetylator genotypes</td>
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<td></td>
<td>Immunosuppression (e.g. HIV infection, lymphoma)</td>
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<td>Concomitant administration of radiotherapy and anticonvulsants (most commonly, those with brain tumors)</td>
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<td>HLA-B*1502: Asians and East Indians exposed to carbamazepine</td>
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<td>HLA-B*5801: Han Chinese exposed to allopurinol</td>
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<td>HLA-A*3101: Europeans exposed to carbamazepine</td>
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SJS and TEN

Mucosal erosions

Non-infectious conjunctivitis
SJS and TEN

SJS and TEN
Sequelae

- Death occurs in every third patient
  - Infections (S. aureus and Pseudomonas aeruginosa)
- Massive transepidermal fluid loss
  - Electrolyte imbalance
  - Inhibition of insulin secretion/insulin resistance
    - Hypercatabolic state
- Complications of TEN best managed in intensive care units.
Sequelae

- Re-epithelialization is complete in most cases within 3 weeks
- Healing is not perfect
  - Symblepharon
  - Conjunctival synechiae
  - Entropion
  - Ingrowth of eyelashes
  - Cutaneous scarring
  - Irregular pigmentation
Sequelae

- Healing Sequelae
  - Eruptive melanocytic nevi
  - Persistent erosions of the mucous membranes
  - Phimosis
  - Vaginal synechiae
  - Nail dystrophy
  - Diffuse hair loss
Treatment of SJS/ TEN

- Early withdrawal of the offending drug is mandatory
- Wound Care:
  - Detached areas, particularly on the back and pressure sites in contact with the bed, should be covered with Vaseline® gauze until re-epithelialization has occurred
  - Serous and/or bloody crusts cleaned daily with isotonic sterile sodium chloride solution
Treatment of SJS/ TEN

- Nostrils cleaned daily with a sterile cotton swab, moistened with isotonic sterile sodium chloride solution, and antibiotic ointment
- Mouth rinsed QID with isotonic sterile sodium chloride solution
- Anogenital region and interdigital spaces short applications of silver nitrate solution (0.5%) in the case of maceration
Treatment of SJS/ TEN

- Ophthalmology consult
  - Eyes cleansed daily with isotonic sterile sodium chloride solution
  - Ophthalmic antibiotic ointment applied to the eyelids
  - Antibiotic eyedrops should be administered three times a day to the cornea
    - reduce bacterial colonization minimize scarring.
Treatment of SJS/ TEN

- 1g/ kg/ day of IVIg for three consecutive days (total dose of 3 g/ kg)
  - Can check stat IGA levels before infusion if available
- No specific therapies for SJS and TEN have shown efficacy in prospective, controlled clinical trials
  - Cyclosporine (3–4 mg/ kg/ day)
  - Cyclophosphamide (100–300 mg/ day)
  - Plasmapheresis, N-acetylcysteine (2 g/ 6 h)
  - TNF-α antagonists (e.g. etanercept, infliximab)
Treatment of SJS/ TEN

APPROACH TO THE PATIENT WITH STEVENS-JOHNSON SYNDROME OR TOXIC EPIDERMAL NECROLYSIS

Stevens-Johnson syndrome or toxic epidermal necrolysis

- Promptly discontinue any, and all, possible offending drugs
- Admit to skilled nursing care unit, e.g. ICU or burn unit
- Correct fluid and electrolyte imbalances
- Caloric replacement
- Protect from secondary infections with topical antibiotic ointments
- Ophthalmology consult and good eye care
- Urology consult if urethral inflammation
- Oral antacids and mouth care
- Pulmonary toilet, if respiratory syndrome
- Periodic cultures of mouth, eyes, skin, sputum
- Physical therapy to prevent contractures
- If extensive denuded areas, use biological dressings or skin equivalents

- Use of intravenous immunoglobulins* (>2 g/kg total dose over 3-4 days)
- Use of other systemic medications on short-term basis

* according to evidence from non-controlled studies performed to date (see section on therapy)

Potentially Dangerous Signs

- Cutaneous: Skin pain, necrosis, bullae/vesicles, mucous membrane changes, palpable purpura, tissue swelling, arthritis

- Rashes of SJS/TEN, DRESS, and morbilliform rashes may all look similar initially

- Other: fever, lymphadenopathy, SOB/wheeze

- Labs: eosinophilia, abnormal LFTs, atypical lymphocytes
References