Medical Dermatology: Bugs and Drugs

Common Skin Infections and Hypersensitivity Reactions

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Disclosures

- None




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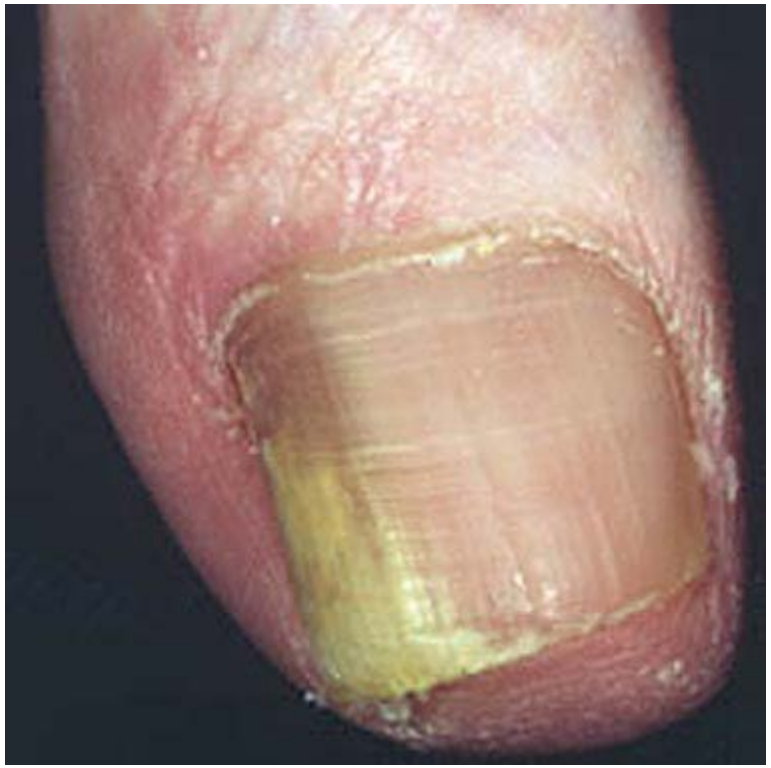
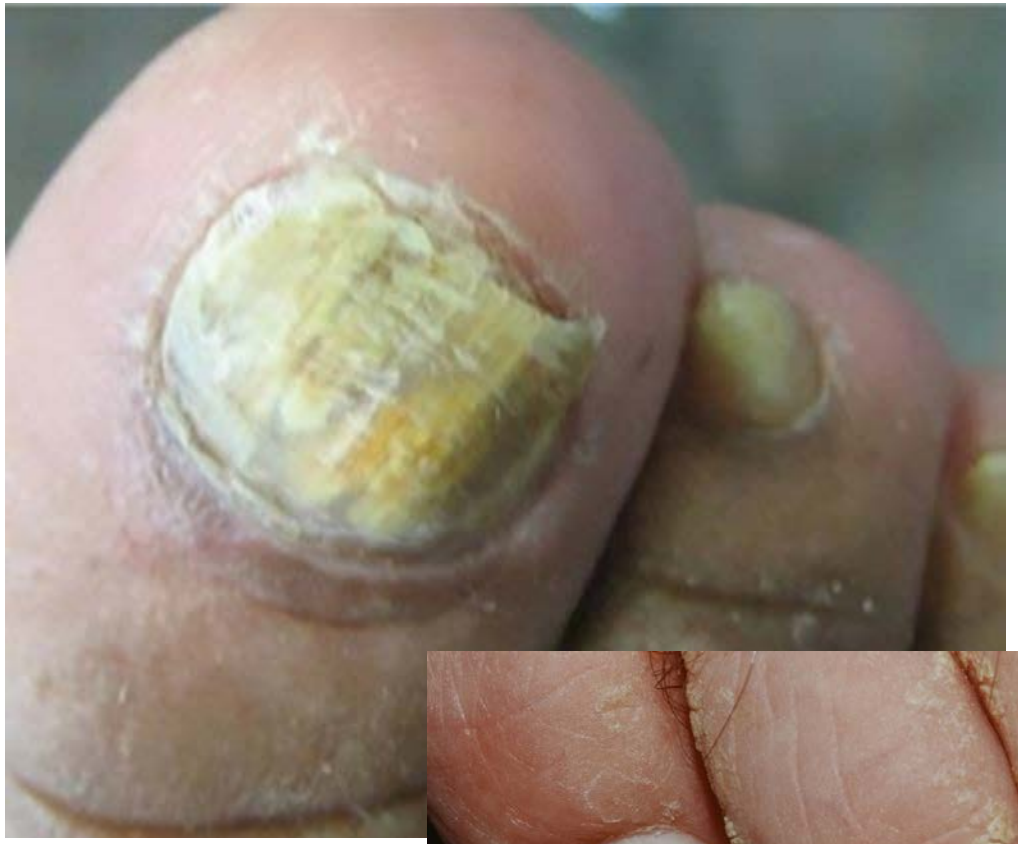
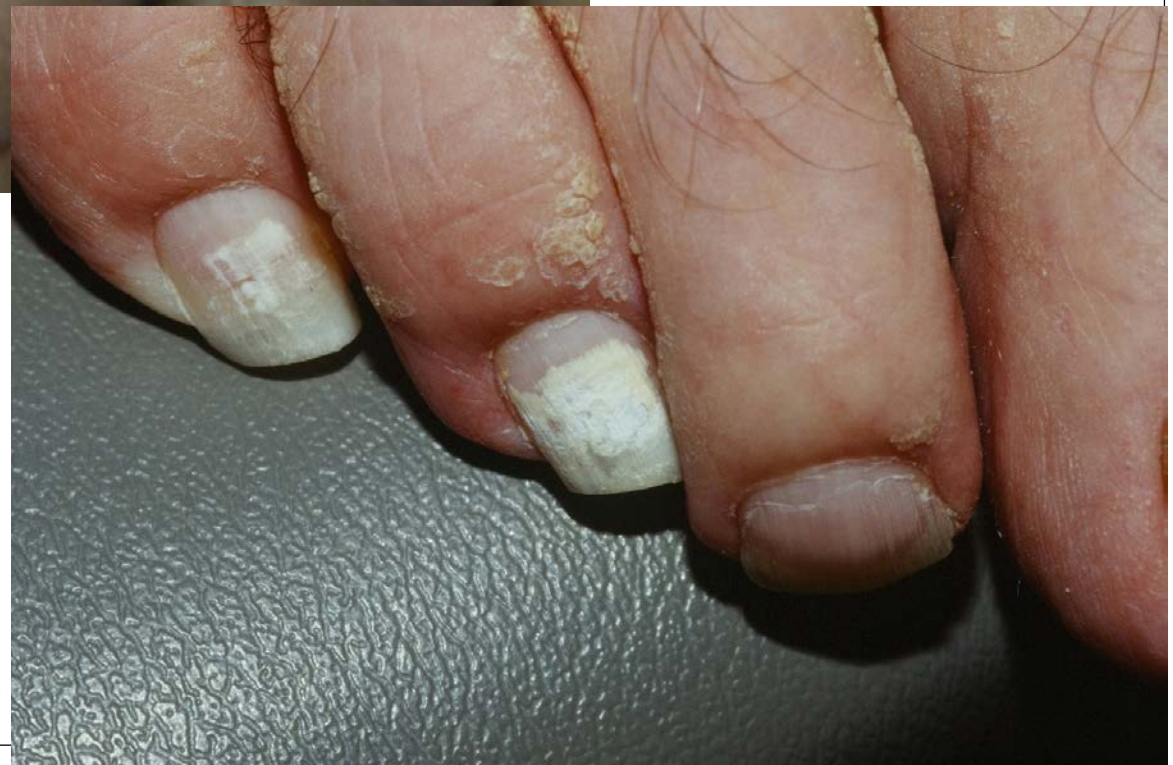
Onychomycosis







Dermatophyte infection:

- Diagnosis
  - Clinical??
  - KOH prep – GOLD STANDARD
  - Culture – would expect – *Trichophyton*, *Microsporum*, and *Epidermophyton* species
- Treatment: tinea faceii, corporis, cruris, pedis, manuum
  - Terbinafine 1% – great coverage for dermatophytes, weak against Candida
  - Clotrimazole 1% – dermatophytes < Candida
  - Econazole 1% – dermatophytes < Candida
  - Ketoconazole 2% – dermatophytes < Candida
  - Ciclopirox 0.77% – dermatophytes < Candida

Dermatophyte infections:

- Systemic therapy:–tinea capitis, folliculitis, or majocchi granuloma
  - Terbinafine , Fluconazole, Itraconazole, Griseofulvin
- Onychomycosis
  - Nail clipping for PAS
  - Systemic - Terbinafine, Fluconazole, Itraconazole, griseofulvin
  - Topical - Ciclopirox (8.5%), Efinaconazole (18%), tavabarole (9%)

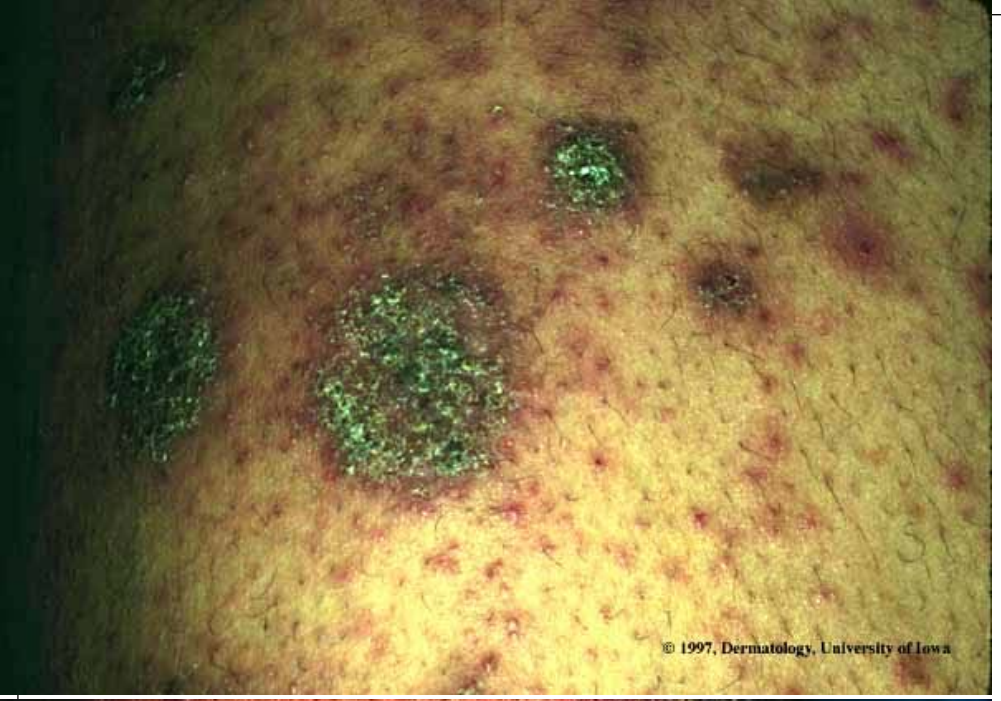
Case

- 22 year old male
- 2 week history of blistering itchy skin eruption on the arms, back, abdomen
- No fever, chills, malaise, oral/mucosal lesions
- No previous treatment
- PMHx: Healthy
- Social Hx: from Texas, college student and athlete

Bullous Impetigo

- Diagnosis:
  - CULTURE!!!
- Typically MSSA
- Where are typical impetigo would be Group A Strep or Staph aureus (MSSA >>MRSA)
- Treatment of choice is for more widespread disease Cephalexin 500 mg BID x 10 days, or 500 mg TID or QID x 7 days (can also consider dicloxicillin)
- For very limited disease can consider topical therapy with mupirocin 2% ointment or cream.

Non-bullous Impetigo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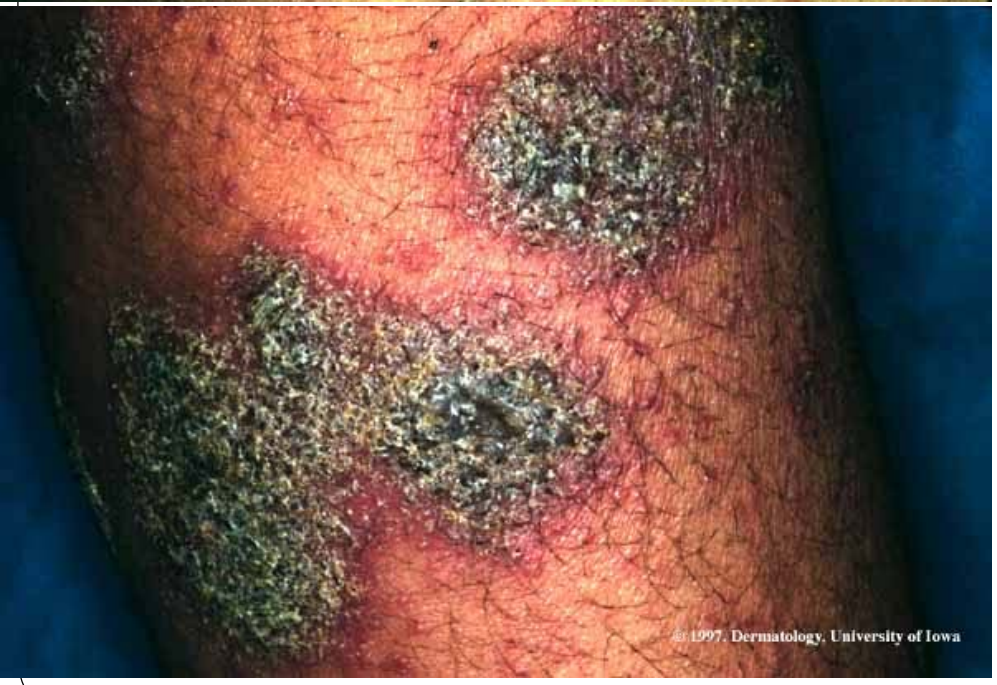
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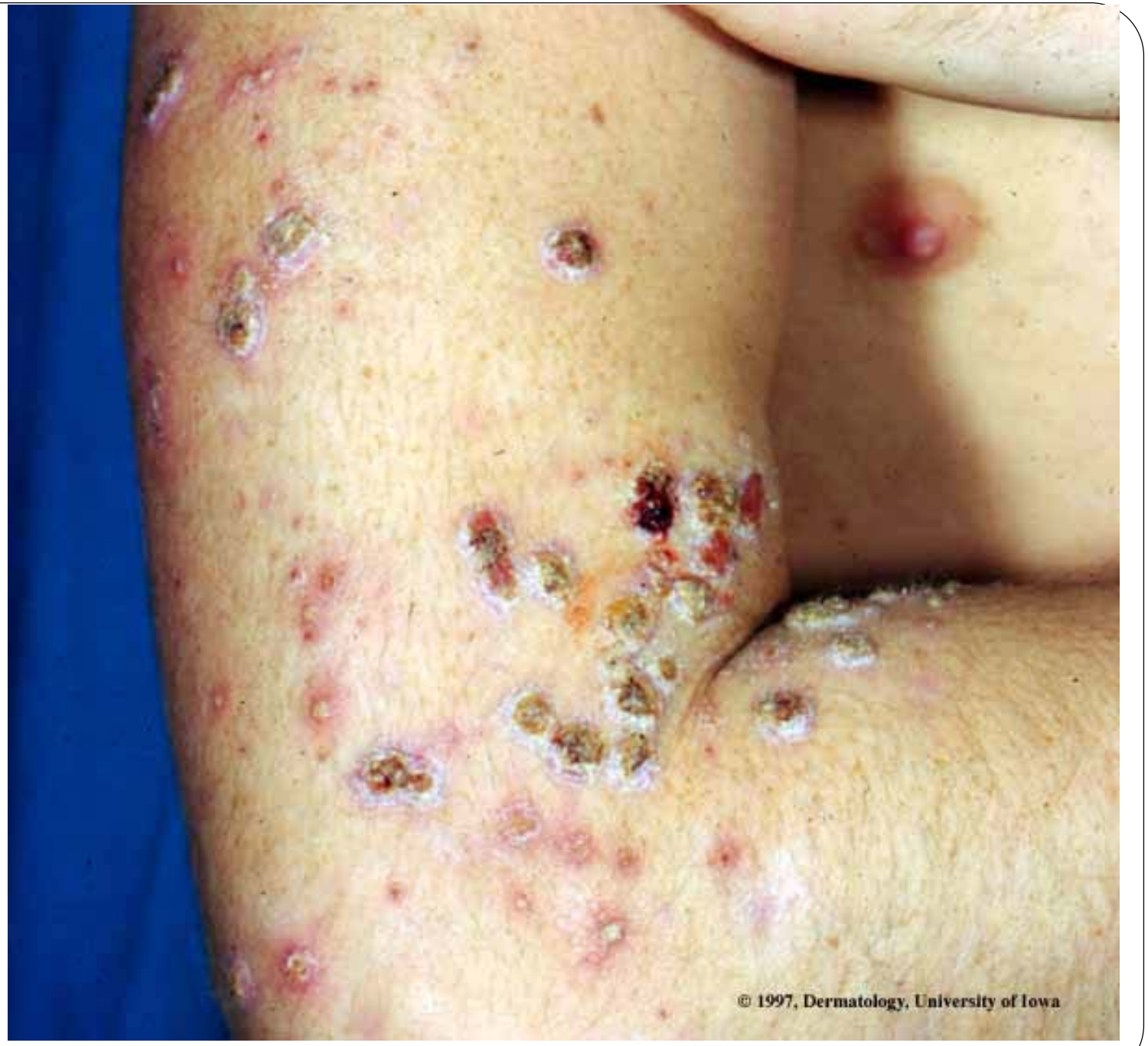
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Case

- 4YOF
- Acute onset of skin redness and blisters on the face, axillae, back 2 days prior. Started as red/dry patch on cheek. Febrile. Malaise . No ocular or oral mucosal involvement. Skin very painful.
- No medications prior to onset
- PMHx: Healthy
- Social Hx: Lives with parents and 7 year old brother.

Staphlyococcal Scalded Skin Syndrome

- Children < 6 years, adults with renal insufficiency
- MSSA predominates there are reports of MRSA (adults > children). All typically from nasopharyngeal colonization but impetigo, pyogenic foci
- **Pathogenesis:**
  - phage group II strains (types 3A, 3C, 55, 71) of *S. aureus*.
  - Exfoliative toxins - ETA (chromosomally encoded), ETB (plasmid encoded), and ETD
    - Glutamate-specific Serine proteases w/very high specificity for Dsg1.
    - Bind extracellular domain of **Dsg1** directly cleave toxins, excreted renally
- **DDX:**
  - sunburn, a drug reaction, Kawasaki disease and extensive bullous impetigo, and, less often, a viral exanthem, toxic shock syndrome, GVHD and pemphigus foliaceus.

SSSS

- **Treatment:**
  - B-lactamase-resistant antibiotics (cefazolin, dicloxacillin, cephalexin) - for minimum of 7 days
  - Wound care with moist occlusion, gentle handling of skin.
- **Prognosis:**
  - Mortality in Children 3% ; Adults ~ 50%
  - Desquamation stops within 3-5 days and re-epithelialization 10-14 days, 7-10 days with proper treatment (wound care + antibiotics)
  - Important to counsel reassure parents that there is no scarring

SSSS

- **Cultures from intact bullae are negative**
- Typically blood cultures are negative
- Sites of colonization or infection:
  - Conjunctiva, nasopharynx, feces, or pyogenic foci
  - Blood cultures are almost always negative in children, but may be positive in adults.
- +/- leukocytosis
- Confirm - frozen sections – AKA Jelly Roll
- slide latex agglutination
- double immunodiffusion
- enzyme-linked immunosorbent assay (ELISA) for toxins

QUESTIONS?

DRUG HYPERSENSITIVITY

Immunology

- Type I
  - IgE dependent drug reactions – urticaria, angioedema, anaphylaxis
- Type II
  - Cytotoxic drug induced reactions – antibody to a fixed antigen i.e. drug-induced pemphigus
- Type III
  - Immune complex dependent drug reactions – serum sickness, vasculitis
  - 10% drug associated - Antibiotics, thiazides, ACE inhibitors, NSAIDS
- Type IV
  - T cell mediated – "delayed-type"
  - Four subtypes IVa, IVb, IVc, IVd
  - Includes
    - Morbilliform, AGEP, **Bullous (SJS/TEN)**, **DRESS,** contact dermatitis, tuberculin reaction

Type IV hypersensitivity reactions - *Internal*

- Hepatitis
- Myocarditis
- Nephritis
- Vasculitis (also in skin)
- Pneumonitis
- Colitis
- Blood cell dyscrasia
  - Neutropenia
  - Thrombocytopenia
  - Anemia
  - Eosinophilia
- Encephalitis
- Drug fever

Type IV hypersensitivity reactions - *Skin*

- **DRESS**
- **SJS/TEN**
- Morbilliform
- AGEP (acute generalized exanthematous pustulosis)
- Allergic Contact (local or systemic)
- Fixed Drug Eruption
- Symmetrical drug-related intertriginous flexural exanthema (SDRIFE, AKA baboon syndrome)

Type IV Drug hypersensitivity

	Immune Mediators	Immune cells	Exanthema
IVa	• Th1 • IFN-γ, TNF-α	• T cells • Macrophages	• Contact dermatitis • Tuberculin rxn
IVb	• Th2 • IL-4, IL-13, IL-5	• Eosinophils	• Morbilliform • DRESS
IVc	• CTL • Perforin • Granzyme B • **Granulysin (SJS/TEN)**	• T cells • NK cells (SJS/TEN)	• Contact dermatitis • Morbilliform (CD4+) • DRESS (CD8+) • SJS/TEN (CD8+)
IVd	• T cells • IL-8 • GM-CSF	• PMN	• AGEP

Morbilliform drug eruption

- Types IVb & Ivc
- Most Common Drugs
  - **Beta lactam Abx, sulfonamides, AEDs, NSAIDS** – many others including herbal medicines
  - Ampicillin/Amoxicillin - Mononucleosis – viral associated
- Clinical Features
  - Onset typically > 4 days after starting medication
  - Urticarial papules, plaques, macules, patches, trunk>extremities, worse in dependent areas
  - Pruritic
  - Can lead to erythroderma and exfoliation.
  - Self limited and may resolve with continued exposure to drug (can treat through if necessary)
  - May not recur with re challenge
  - No fever
  - No internal organ involvement
  - Histology not specific
- Treatment – dc drug, topical vs systemic steroids, antihistamines

Morbilliform drug eruption

- Work up – mainly to differentiate from DRESS
- CBC with diff, BUN, Cr, Liver enzymes, Troponin, CK, Amylase, lipase

Case

- 28 year old - IVDU
- Readmitted after being started on vancomycin for MRSA endocarditis, with fever, chills, and a new rash
- Vancomycin x 3 weeks
- CBC with elevated WBC and eos > 1500

Case

- 82 year old
- Recent medications within 4-8 weeks – allopurinol and nifedipine
- Hospitalized – allopurinol stopped – nifedipine continued
- Rash, fever, eosinophilia, persistent after discharge

DRESS

- Type IVb & IVc *(same as morbilliform)*
- Drugs:
  - **carbamazepine**, phenobarbital, phenytoin, allopurinol, TMP/SMX, dapsone, minocycline, gold salts, strontium ranelate, vancomycin, ***lamotrigine***, nevirapine, sulfasalazine, hydroxychloroquine, ibuprofen, Proton pump inhibitors
- Clinical Features
  - Onset *typically* after 2-6 weeks of continuous drug therapy.
  - Fever, lymphadenopathy, eosinophilia, atypical lymphocytes, nephritis, myocarditis, hepatitis, myositis, pancreatitis, thyroiditis, colitis
  - Skin eruption = **variable**, typically morbilliform, but can be targetoid, bullous, pustular.
  - Reactivation of human herpesviruses (HHV4-7)
  - Resolves within 2-6 weeks after cessation of medications
- Mortality – **5-10%**

Table 1 Scoring System for Classifying DRESS Cases as Definite, Probable, Possible, or No Case, from Kardaun et al[11]

Score	−1	0	1	2
Fever ≥38.5°C	No/U	Yes		
Enlarged lymph nodes		No/U	Yes	
Eosinophilia		No/U		
Eosinophils			0.7-1.499 × 10^9 L^{-1}	≥1.5 × 10^9 L^{-1}
Eosinophils, if leukocytes <4.0 × 10^9 L^{-1}			10%-19.9%	≥20%
Atypical lymphocytes		No/U	Yes	
Skin involvement				
Skin rash extent (% body surface area)		No/U	>50%	
Skin rash suggesting DRESS	No	U	Yes	
Biopsy suggesting DRESS	No	Yes/U		
Organ involvement*				
Liver		No/U	Yes	
Kidney		No/U	Yes	
Muscle/heart		No/U	Yes	
Pancreas		No/U	Yes	
Other organ		No/U	Yes	
Resolution ≥15 days	No/U	Yes		
Evaluation of other potential causes				
Antinuclear antibody				
Blood culture				
Serology for HAV/HBV/HCV				
Chlamydia/mycoplasma				
If none positive and ≥3 of above negative			Yes	

DRESS = Drug Reaction with Eosinophilia and Systemic Symptom; U = unknown/unclassifiable; HAV = hepatitis A virus; HBV = hepatitis B virus; HCV = hepatitis C virus.

*After exclusion of other explanations: 1, one organ; 2, two or more organs. Final score < 2, no case; final score 2-3; possible case; final score 4-5, probable case; final score > 5, definite case.

2-3= possible, 4-5 probable, > 5 definite

DRESS: *Internal organ involvement*

- **Hepatitis**
  - Most common – typically self limited
  - **can be fulminant and fatal – most common cause of death in DRESS**
  - Less responsive to steroids – may need higher doses
- **Nephritis**
  - Common, self limited
  - Can be fulminant leading to chronic renal failure and death
  - Less responsive to steroids
- **Thyroiditis**
  - Case reports in patient with chronic DRESS
- **Pancreatitis**
  - Less common than hepatitis or nephritis
  - Associated with delayed T1DM
  - Transient elevations of amylase/lipase

DRESS: *Myocarditis*

- Numerous case reports -- **<u>Mortality up to 50%</u>**
- Acute eosinophilic myocarditis (hypersensitivity myocarditis)
  - May go undetected
  - cardiac enzymes **not** always elevated
  - **Pro-BNP**
  - Non-specific S-T segment or T-wave abnormalities, sinus tachycardia, conduction delay
  - Systolic dysfunction
  - Sudden cardiac death
- Acute necrotizing eosinophilic myocarditis (ANEM)
  - More severe
  - Chest pain, ST segment elevation, ↑cardiac enzymes
  - ↓systolic function, biventricular failure, ↑mm wall thickness
- Median 14 days, Mean 35 days, & up to 4 months after dx
- Typically responds best to treatment with corticosteroids
- **Renal and liver toxicity of most common cause of mortality but cardiac toxicity has highest mortality rate**

DRESS – *approach to patient*

- CBC with diff, LFT, BUN, Cr, CK, Troponin, Amylase, Lipase, Pro BNP
- EKG & ECHO
- Case reports of T1DM and auto-immune thyroiditis
  - monitor TSH, T3, T4, and glucose
- Patients need to be followed closely with repeat labs during and after treatment phase
- I always counsel about the possibility of cardiac involvement, especially during the first 2 weeks after diagnosis (70% develop within 2 weeks of dx.)

DRESS: *Treatment*

- Stop all possible offending medications
- Corticosteroids:
  - Start at 1 mg/kg with slow taper (2-6 months)
  - Doses likely higher if inpatient - solumedrol 1 gram daily for cardiac/renal involvement, 250 mg IV x 3 days for others
  - All followed by oral slow taper of prednisone
- Others:
  - Cyclosporine
  - IVIG
  - Mycophenolate mofetil
  - Rituximab, azathioprine, plasmapheresis

DRESS: *Conclusions*

- DRESS typically develops after 2 weeks of continuous therapy
- Early recognition and diagnosis of and treatment DRESS is related to decreased morbidity and mortality
- DRESS is caused by many common medications
- Renal and Hepatic failure most common cause of mortality
- Myocarditis is an under recognized and potentially fatal complication of DRESS with the **highest mortality rate**

SJS/TEN

- **Clinical presentation**
  - Fever
  - Flu-like symptoms x 1-3 days
  - Photophobia, conjunctival itching, dysphagia, painful skin
  - Present with quick onset (~3 days) - symmetric burning/pain of skin followed by dusky macules, patches with epidermal detachment – **including mucous membranes**

- **Diagnosis**
  - Clinical
  - Skin biopsy for H&E and direct immunofluorescence

SJS/TEN

- **Type IVc**
  - Granzyme B, perforins, **Granulysin** → keratinocyte apoptosis
    - Granulysin – now thought the be the main contributing factor
    - Drug-Specific CD8 T-cells and NK cells
    - MHC-1 and T cell receptors → clonal expansion of cytotoxic T-cells
- 2-13 per million/year

- **Risk Factors**
  - HIV – **100** times general population
  - Autoimmune disease – **50X** in SLE
  - Active malignancy (hematologic) – **50**X

SJS/TEN

- **Drugs:**
  - Antibiotics – **50%** - TMP/SMX, B-lactams, Fluoroquinolones
  - Antiepileptic/mood stabilzers – 24% lamotrigine, phenytoin, carbamazepine
  - Allopurinol
  - NSAIDS - oxicam
  - Others: nevirapine, modafinil, minocycline, **PPIs**
  - Typically within 1-3 weeks (avg 14 days)
  - Unlikely after first 8 weeks

SJS/TEN

- Mortality:
  - SJS < 10%
  - SJS/TEN 10-30%
  - TEN > 40%
- Treatment:
  - Burn unit and supportive care
  - Multidisciplinary consultation – Dermatology, Ophthalmology, Urology, OB/GYN
  - Corticosteroids – early may increase survival
  - Cyclosporine
  - Etanercept (TNF alpha inhibitors)
  - IVIG?

HLA TYPES & DRUG ERUPTIONS

- HLA-B*1502
  - Carbamazepine & phenytoin - SJS/TEN
  - FDA recommends screening for pts from: **Taiwan, China, Thailand, Indonesia, Malaysia, Philippines, & India** prior to starting medication
- HLA-B*0206
  - SJS/TEN with severe ocular involvement
- HLA-A*3101
  - European descent – SJS/TEN
  - Japanese – DRESS, SJS/TEN
  - Consider screening prior to starting carbamazepine
- HLA*5701
  - Abacavir hypersensitivity
- HLA-B*5801
  - Allopurinol-induced SJS/TEN or DRESS
  - Han Chinese in Taiwan

SJS/TEN: *Conclusions*

- SJS/TEN is a subtype of Type IV drug hypersensitivity
- **Mortality of 20-25%**
- Antibiotics, AEDs/mood stabilizers, allopurinol, NSAIDS are common inciting medications
- Uncommon after 8 weeks of therapy
- Early diagnosis and treatment in an experienced burn unit provide are the standard of care and decrease morbidity and mortality

Questions?

- THANK YOU!!!
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