Cutaneous Drug Eruptions

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Disclosures

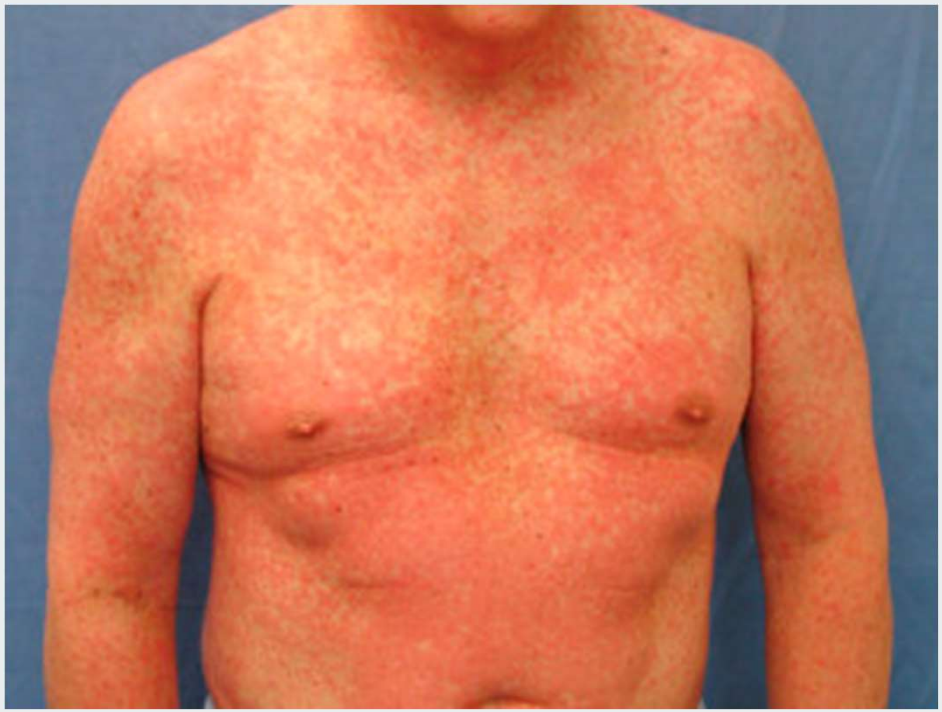
I have no financial interests to disclose.

Some treatments I will talk about are “off-label.” However, they are generally accepted as treatments in the dermatology community with supporting evidence-based research.

Objectives

- Explain common morphologies of various drug reactions.
- Identify common drugs that cause cutaneous rashes.
- Identify cutaneous manifestations that would be considered a dermatology emergency related to taking a drug.

Maculopapular or Morbilliform Drug Reactions



Of the following locations, which area will you NOT see a morbilliform drug eruption:

A) Abdomen, back, chest

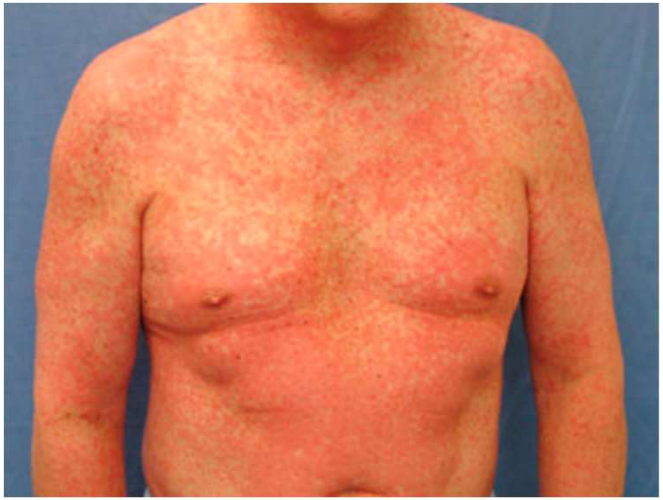
B) Mucous membranes, hair or nails

C) Palms and soles

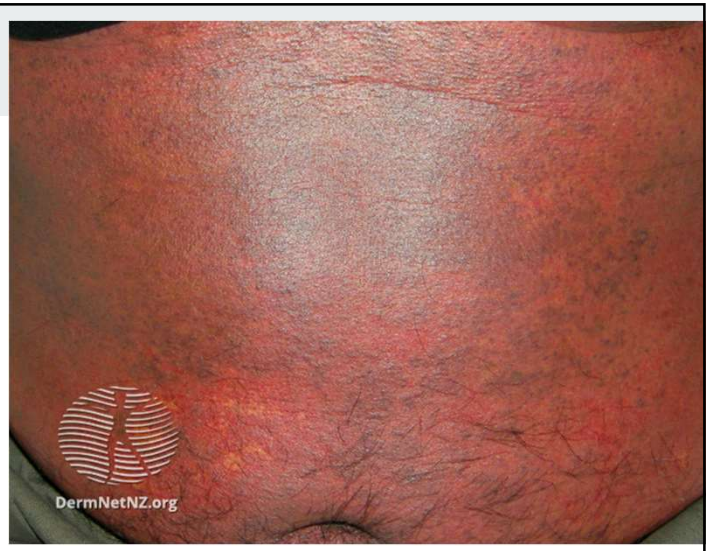
D) Upper and lower extremities

Maculopapular or Morbilliform Drug Reactions

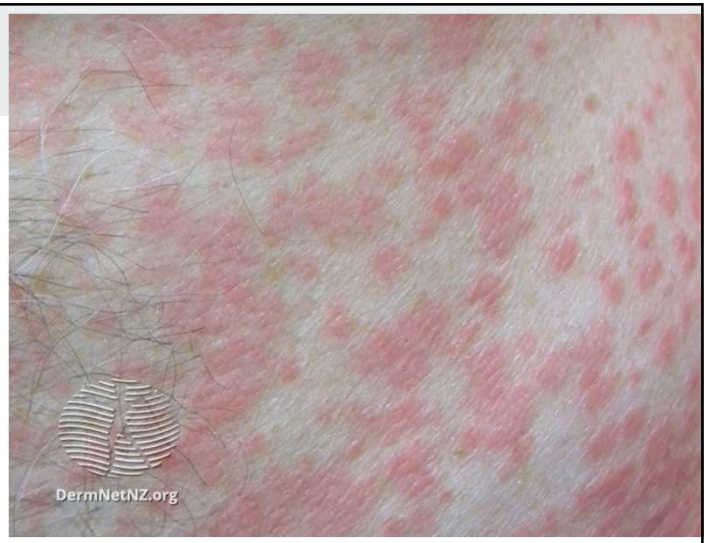
- **Most common drug rash seen** in day to day practice
- Type IV immune reaction mediated by cytotoxic T-cells.
- DDX = viral exanthems (looks the same)
- Occurs in up to a 5% of drug naive patients
- Increased risk in HIV + and bone marrow transplant patients



Morbilliform Drug Reactions



- Multiple discrete, diffusely scattered erythematous or violaceous macules and scaly papules.
- May see targetoid lesions.
- May involve the palms and soles but typically not seen on the face.
- Will NOT involve the mucous membranes, hair/nails.
- Will NOT have blistering, pustules but may see diffuse scaling or exfoliation in later stages.
- Starts 4 days to 3 weeks after starting the drug
- May have itching and fever



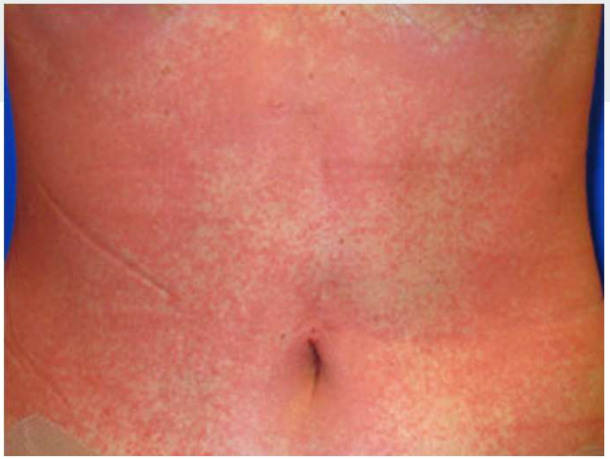
Morbilliform Drug Reactions

Most common drug causes:

- beta-lactam antibiotics - penicillins (PCN) and cephalosporins
- Sulfonamides - sulfamethoxazole and trimethoprim (Bactrim)
- Allopurinol
- Anti-epileptic drugs
- **In general, these are the most common drugs to cause rashes.**

More possible drug culprits

- Allopurinol
- Amoxicillin
- Amphotericin B
- Ampicillin
- Barbiturates
- Captopril
- Carbamazepine
- Chlorpromazine
- Diflunisal
- Enalapril
- Gentamicin
- Gold salts
- Isoniazid
- Meclofenamate
- Naproxen
- Oral hypoglycemic agents
- Penicillin
- Phenothiazines
- Phenylbutazone
- Phenytoin
- Piroxicam
- Quinidine
- Sulfonamides
- Thiazides
- Thiouracil
- Trimethoprim–sulfamethoxazole



Morbilliform Drug Reaction: Treatment

- Will resolve 1-3 weeks after drug is stopped.
- If it's not stopped, it could progress to an exfoliative dermatitis that could cause difficulty with thermoregulation.
- Topical steroid treatment
  - Widespread: Triamcinolone 0.1% ointment BID for 2 weeks
  - Newer, not widespread: Betamethasone/Clobetasol BID for 2 weeks
- Wet wraps may be helpful
- Prednisone (in some cases)

A note on prednisone

Lots of associated side effects:

- Avascular Necrosis
- GI bleeding
- Osteoporosis
- Hyperglycemia
- Psychosis and other psychological side effects
- Cardiac: Heart failure, HTN, MI, CVA
- Infections
- Acne
- Insomnia
- Ophthalmic - glaucoma and increased risk of cataracts

Koshi, E. J., Young, K., Mostales, J. C., Vo, K. B., & Burgess, L. P. (2022). Complications of Corticosteroid Therapy: A Comprehensive Literature Review. *The Journal of pharmacy technology : jPT : official publication of the Association of Pharmacy Technicians*, *38*(6), 360–367. https://doi.org/10.1177/87551225221116266

Medical Legal implications

- High amounts of money paid out in lawsuits to patients with poor outcomes from prednisone
  - $25K - 8.1 million
- Lawsuits - top 3 reasons
  - Avascular necrosis - most common
  - psychosis or mental changes
  - vision changes
- Most commonly sued - dermatologists (12%), PCPs (10%)
- Need to document risks and counsel patients

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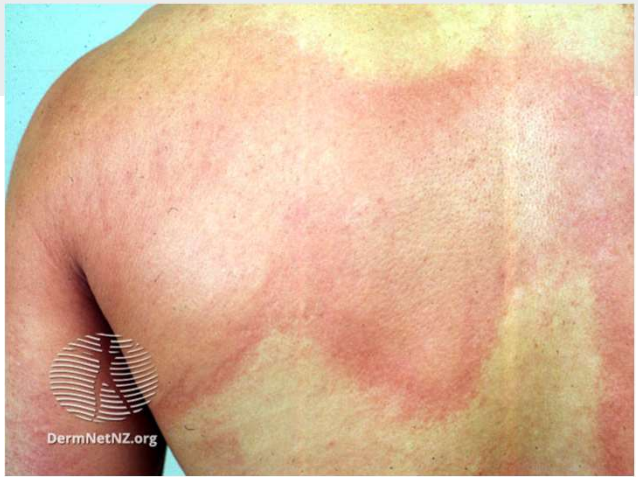
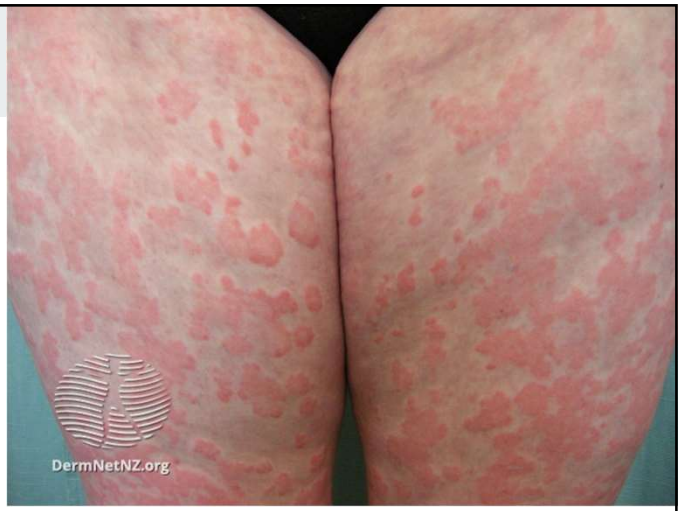
Urticaria



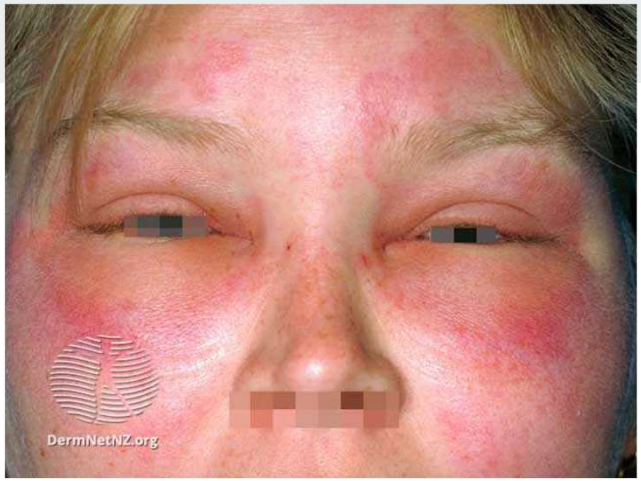
Urticaria

- Edematous, erythematous, smooth plaques (wheals) ranging from a few mm to several cm
  - Usually symmetric and diffuse/scattered on the skin
  - Do NOT have scale
- Last less than 24 hours
- Often pruritic
- Commonly caused by drugs: PCN, cephalosporins, Aspirin, blood products, monoclonal antibodies



Urticaria Basics

- Histamine, platelet-activating factor and cytokines activate sensory nerves.
- This activation causes blood vessel dilation and leakage of fluid into surrounding tissues.
- Angioedema is caused by the release of Bradykinin.
- Three types of drug-induced urticaria:
  - anaphylactic and accelerated reactions
  - nonimmunologic histamine release
  - serum sickness.



Angioedema

- A form of urticaria
  - But the swelling occurs in the deep dermis, subcutaneous layers of the skin and the mucous membranes
- Locations: perioral area/lips, eyelids, hands, feet, genitalia, tongue, uvula, soft palate, or larynx
- Can be life-threatening
- Treatment can range from oral antihistamines to epinephrine and hospitalization

Anaphylactic and accelerated

- Cause by immunologic histamine release
- IgE mediated
  - IgE-induced mast cell degranulation = anaphylaxis
- Occurs within minutes to hours of exposure to drug
- PCN family is most common cause
- Radioallergosorbent (RAST) testing can be helpful to determine if a patient is allergic but not completely reliable.
  - 50% of pts with a + RAST to PCN will develop anaphylaxis
  - ~97% of pts with a negative RAST to PCN will not develop anaphylaxis
- Cross sensitivity in the cephalosporin family (mostly 1st and 2nd generations)
- Hives can be a sign of potential anaphylaxis so want to avoid PCN in those pts.

Serum Sickness

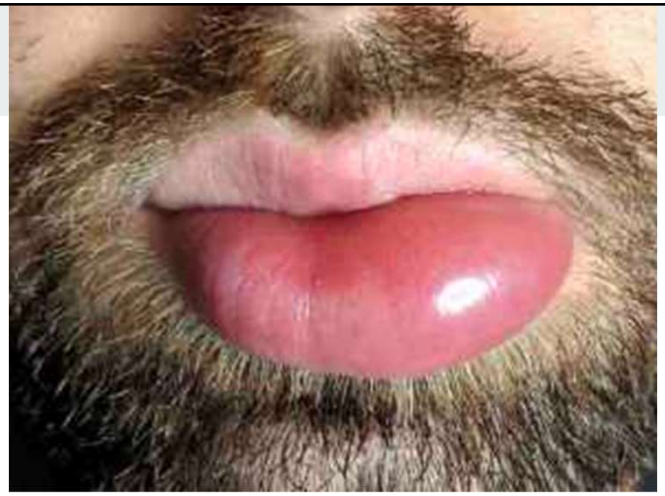
- Type III or immune complex reaction
- Potent inflammatory response caused by a decrease in serum levels of C3 and C4.
- Urticaria occurs 8-13 days after drug exposure
- May have just urticaria or a morbilliform rash
- Locations: trunk or throughout the body (may include hands and feet)
- Systemic symptoms: fatigue, malaise, lymphadenopathy, fever, GI symptoms, joint pains

Serum Sickness

- Labs: WBC elevated (up to 25,000)
- Proteinuria is common
- DIF skin biopsy: IgM, IgE, IgA, or C3 can be +
- Drug culprits: Penicillin, sulfa drugs, thiouracils, cholecystographic dyes, hydantoins, aminosalicylic acid, and streptomycin
- Treatment: Stop the drug, antihistamines, steroid taper

Non IgE-induced Urticaria

- Nonimmunologic reactions (no immune response)
- Occurs 30 minutes to 24 hours after drug exposure
- Urticaria and/or angioedema may occur
- Itching, flushing are common
- Causative agents: Aspirin, NSAIDs, contrast dye, opiates, polymyxin B, lobster, and strawberries
- Treatment: antihistamines
    - Doxepin for contrast dye



Angioedema in ACEIs

- Angioedema caused by Angiotensin-converting enzyme inhibitors (ACEIs)
- Probably not immune mediated
- ~ 0.1% to 2.2% rate of occurrence for patients on an ACEI
- Captopril is shorter acting so the angioedema is less severe and can be managed with antihistamines or oral steroids
- Lisinopril and enalapril reactions can be more severe and life threatening.

Dermatology Emergencies

Dermatology Emergencies

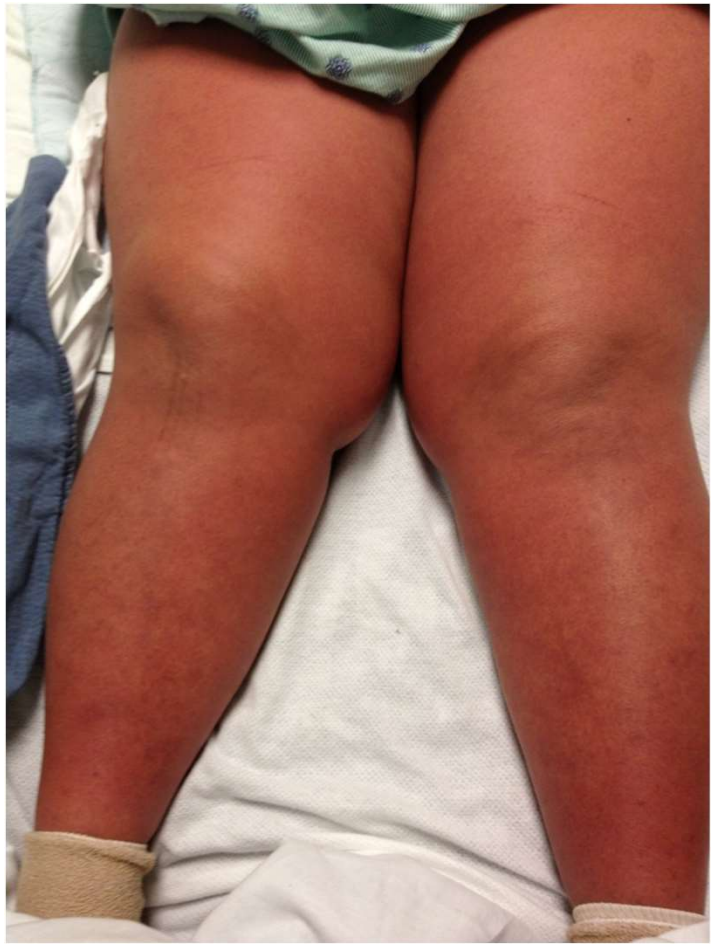
- Stevens–Johnson syndrome (SJS)
- Toxic epidermal necrolysis (TEN)
- Drug reaction with eosinophilia and systemic symptoms (DRESS)
- Acute generalized exanthematous pustulosis (AGEP)

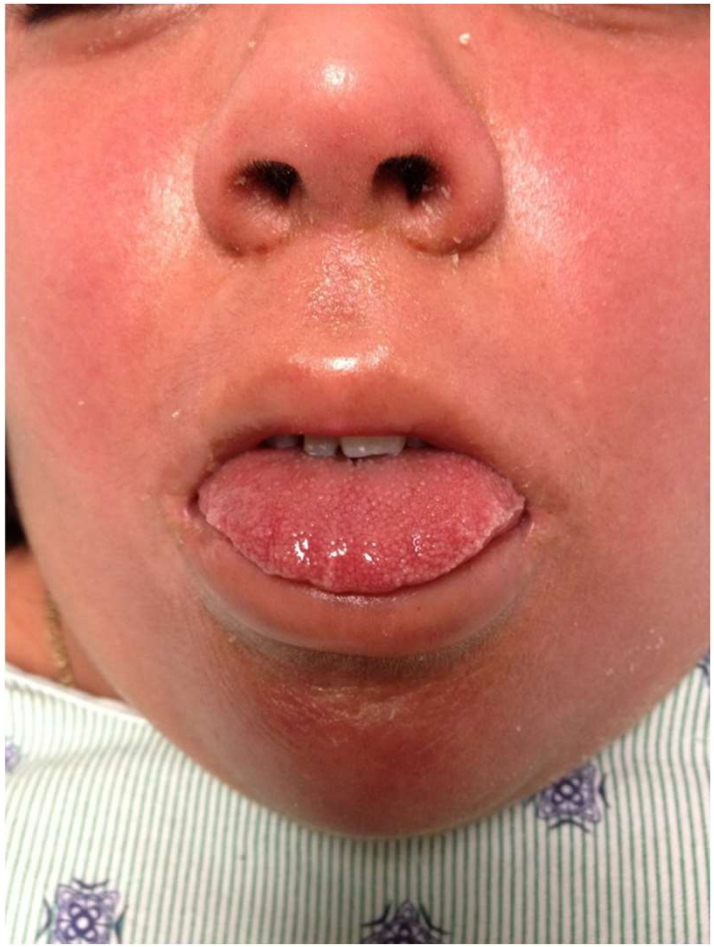
- Rare but must not be missed!

Drug reaction with eosinophilia and systemic symptoms (DRESS)

DRESS

- Up to 10% fatality rate → mostly as a result of fulminant hepatitis with hepatic necrosis
- **30% of cases have eosinophilia (onset can take 1-2 weeks)**
- **Prodrome of fever (38-40 degrees celsius)**
- Other systemic features: lymphadenopathy, arthralgias, hepatitis, pneumonitis, thyroiditis, GI bleeding
- At least one organ involved - most commonly the liver





DRESS

Photos - courtesy of Dr. Michael Leslie

DRESS Presentation

- Rash morphology: morbilliform
  - edematous morbilliform papules with follicular differentiation
- **Initial locations** - face, trunk, extremities.
  - Can spread throughout the body and cause exfoliative dermatitis
- Facial edema in 25% of cases
- Other morphologies: vesicles, bullae, pustules, erythroderma, purpura (EVERYTHING!!!!)
  - Can have mucosal involvement but infrequent

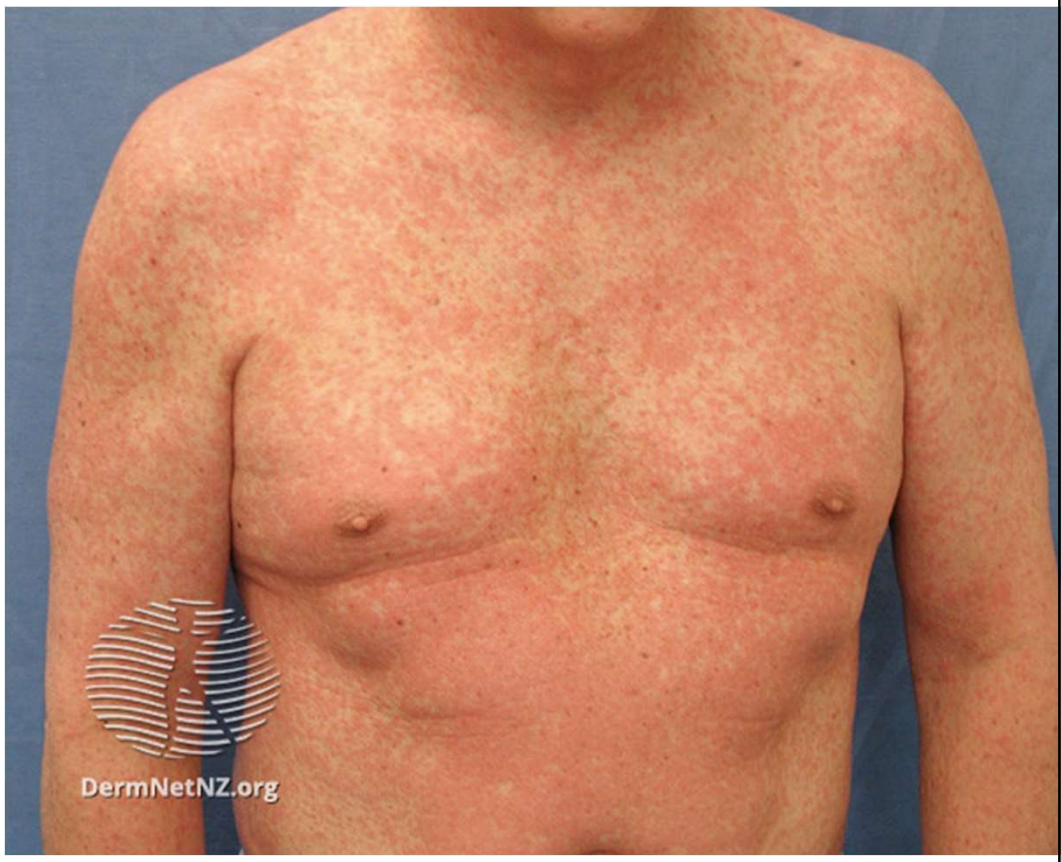
DRESS Cont.

- Occurs: 15-40 days after drug exposure
- Labs: eosinophilia (really high), lymphocytosis, increased LFTs
  - activation of latent or new infection with human herpesvirus 6 (not a routine test)
- Course: rash may persist for weeks to months

DRESS Drug Causes

MOST COMMON:

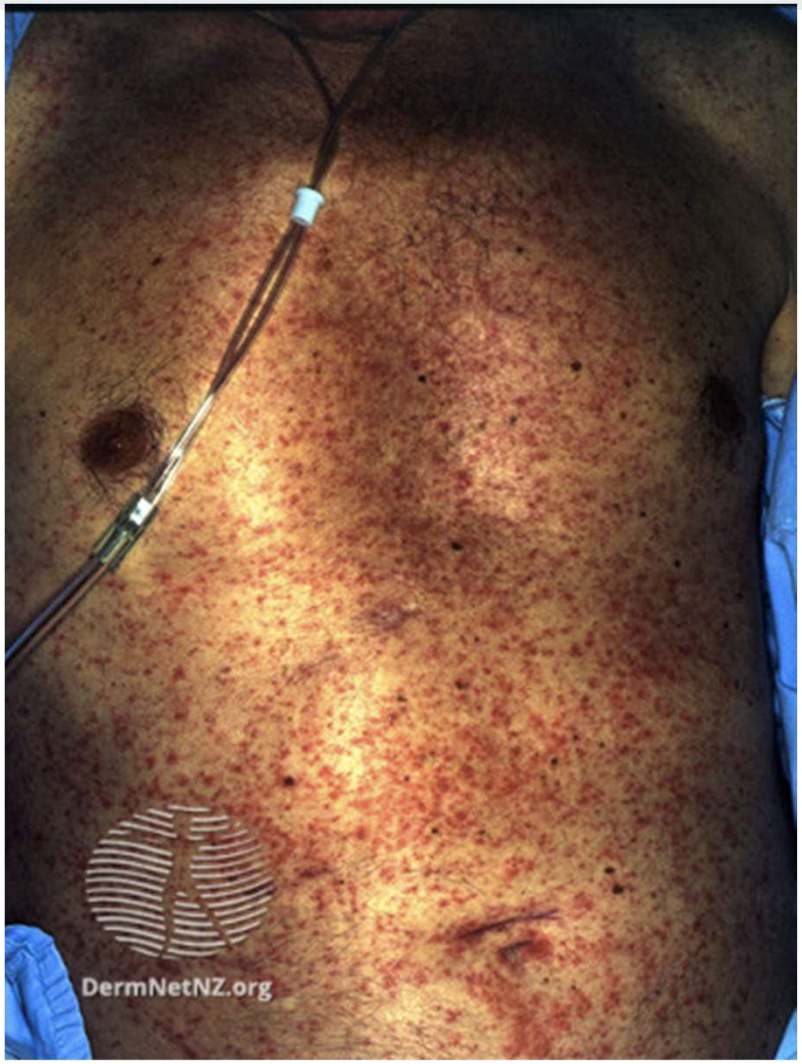
- **Aromatic anticonvulsants (especially phenytoin, carbamazepine, and phenobarbital)**
- **sulfonamides (dapsone and sulfasalazine)**
- Allopurinol
- Antiretrovirals (abacavir, nevirapine)



DRESS Cont.

DDX:

- Viral exanthem
- SJS/TEN/AGEP
- Cutaneous lymphoma
- Idiopathic hypereosinophilic syndrome



DRESS Treatment

- REFER TO ED if you suspect DRESS
- Very long taper (months) of oral steroids
  - if stopped too soon, DRESS can rebound
- Systemic evaluation and appropriate treatment
- Topical steroids can help cutaneous symptoms

Stevens-Johnson Syndrome (SJS) and Toxic Epidermal Necrolysis (TEN)

SJS and TEN

- **SJS and TEN are the same disease but are on a continuum.**
- SJS - < 10% BSA involvement
- SJS/TEN overlap - 10-30% BSA
- TEN - >30% BSA
- Mortality rate for SJS: up to 5%
- Mortality Rate for TEN: 25-35%

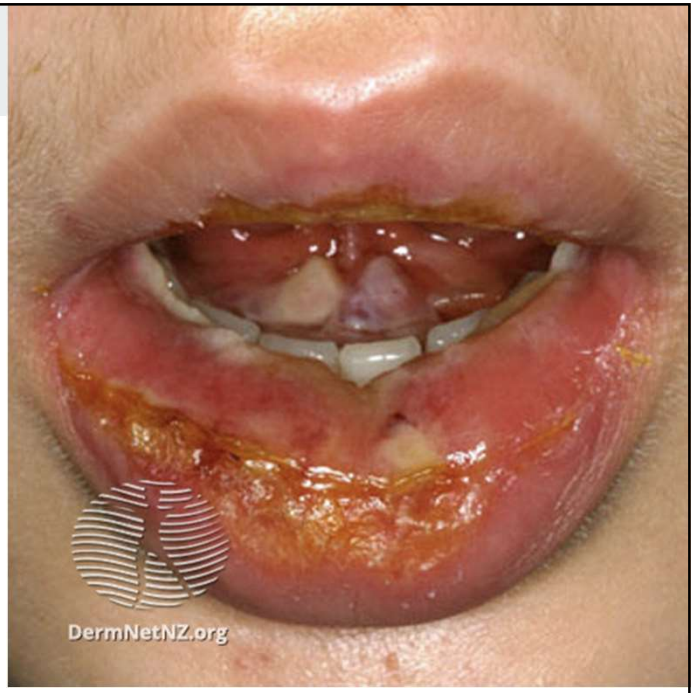
SJS/TEN

Etiology → It's a combination:

- chemical structure of the drug,
- genetics (HLA type alleles)
- drug metabolism
- T lymphocyte clones

- Immunocompromised patients have a higher risk.
- Extremely Rare but a true derm emergency.

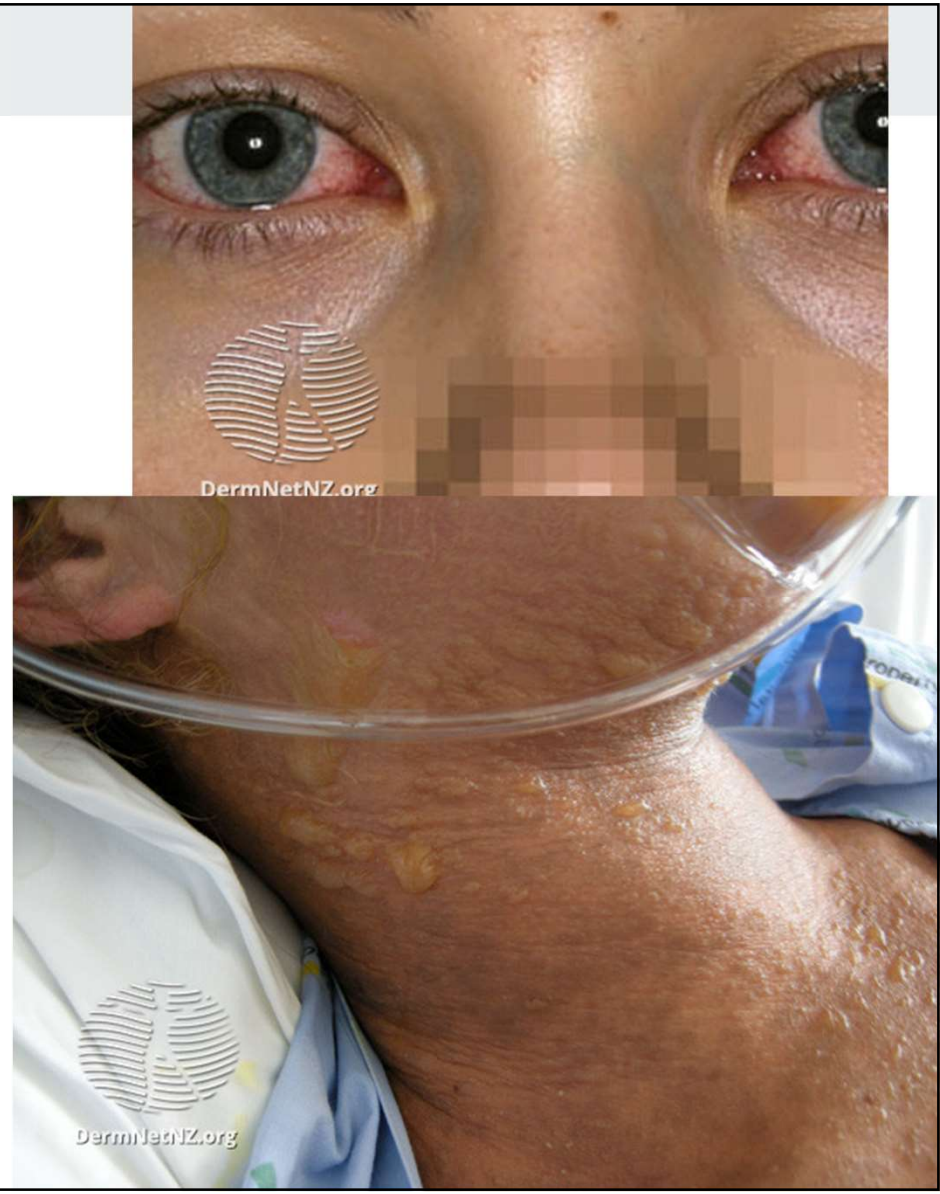
SJS Presentation



- Occurs 7-24 days after drug exposure
- Prodrome (1-3 days prior to skin findings): URI symptoms, fever, skin pain
  - Eye pain too - always ask about scratchy feeling eyes
  - Pain with swallowing
- Lesions Appears on the trunk first
  - Then spreads to face, neck and upper extremities
- May see palmar or plantar involvement before the trunk
- Ocular, buccal or genital mucosa involved 90% of the time

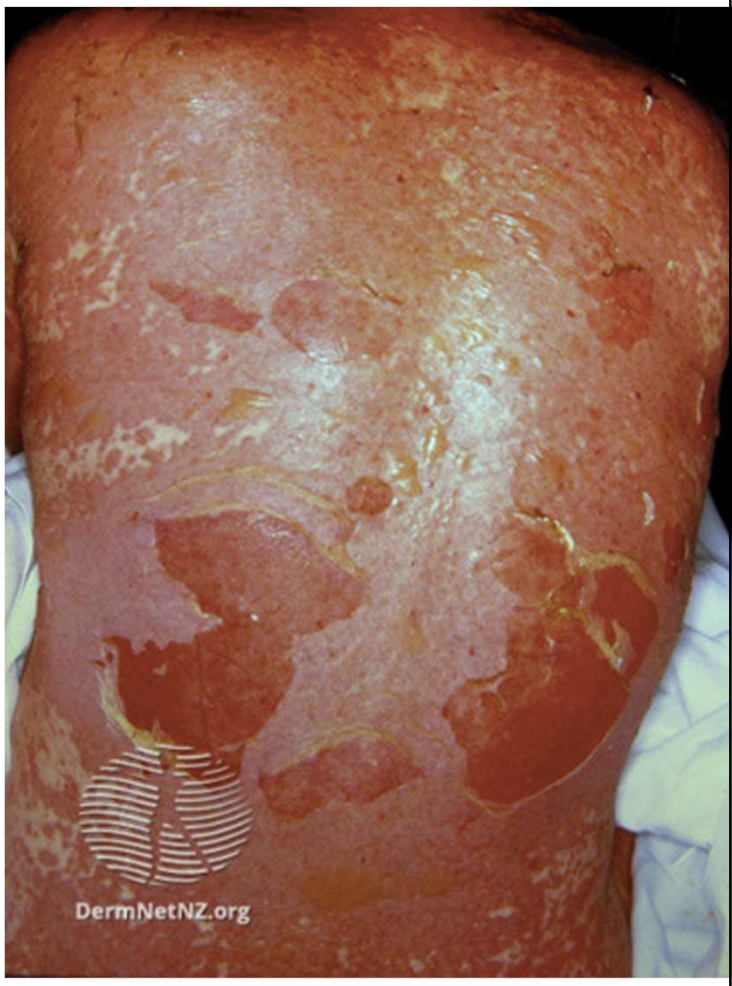
SJS Presentation

- Painful bullae and erosions
- Macular lesions can start as a dusky red or purple, then turn grey within hours to days
- Then, the epidermis becomes necrotic to form blisters (bullae)
- Nikolsky sign: flaccid blisters easily torn and extend sideways with slight thumb pressure



SJS → TEN

- Can also have systemic symptoms: fever, lymphadenopathy, hepatitis, leukopenia, erosions of the GI and respiratory tracts.
- TEN involves a greater BSA so patients decompensate
- Bullae are frail and leave sheets of the epidermis exposed.
- Causes difficulties with temperature regulation and patients require burn treatment care.
- Complications: fluid and electrolyte imbalances, infection, respiratory decompensation due to sloughing of the respiratory tract

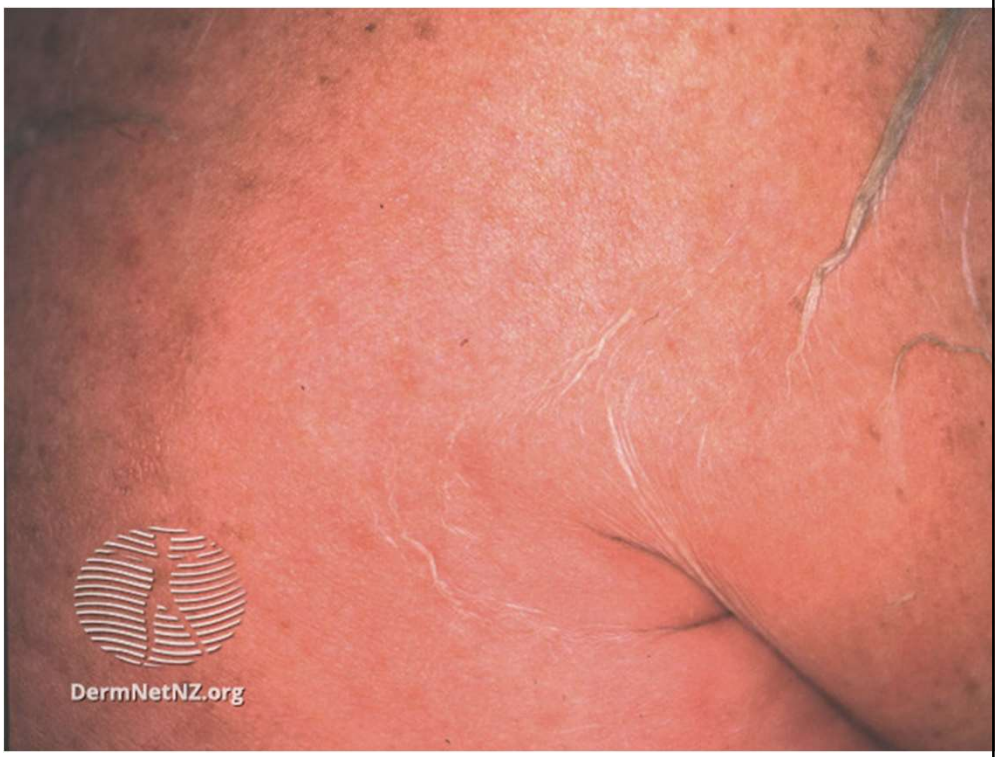


Associated Drugs

- Nevirapine
- Lamotrigine
- **Anticonvulsants: Carbamazepine, Phenytoin, Phenobarbital**
- **Antibiotics: Co-trimoxazole and other anti infective sulfonamides (BACTRIM and SEPTRA)**
  - **Also aminopenicillins, cephalosporins and quinolones**
- Sulfasalazine
- **Allopurinol**
- **NSAIDs**
- Antiretroviral drugs
- Checkpoint inhibitors: ipilimumab, nivolumab (often used in derm for MM)

DDX

- SSSS
- Generalized bullous fixed drug eruption
- Autoimmune blistering diseases
- Bullous phototoxic reactions
- AGEP
- DRESS
- Erythema multiforme major
- Kawasaki Disease
- Severe GVHD

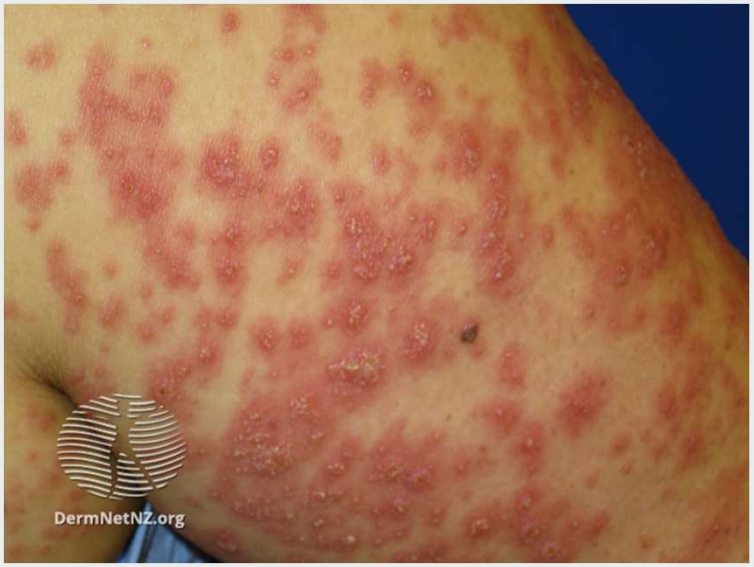


Treatment

- STOP THE DRUG
- Transfer of care to ICU or Burn Unit
- Oral steroids are not recommended and remain controversial
- IVIG
- Etanercept
- Cyclosporine

- Prevention: Guidelines now recommend genotyping Asians before starting carbamazepine and all Asians and African Americans before starting allopurinol

Acute Generalized Exanthematous Pustulosis (AGEP)



Acute Generalized Exanthematous Pustulosis (AGEP)

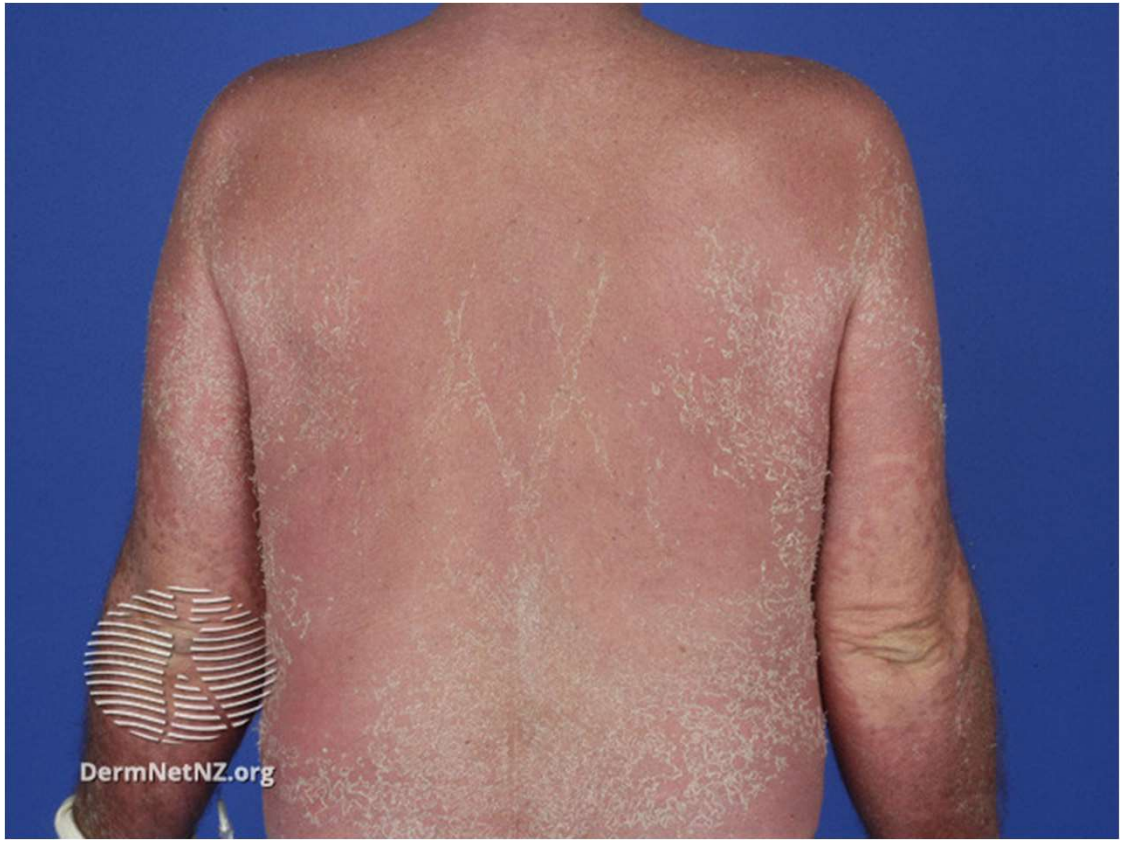
- Onset is fast: <4 days from drug exposure
- Many scattered, sterile pustules with background erythema and edema
  - sometimes facial edema
- Face, intertriginous areas have initial lesions, then spreads
- 50% get petechiae, purpura, targetoid lesions or vesicles
- Fever is common, itching or burning skin
- Can see leukocytosis with neutrophilia, transient renal abnormalities, hypocalcemia.
- Skin biopsy is fruitful

AGEP

DDX: DRESS, TEN, generalized pustular psoriasis

Treatment:

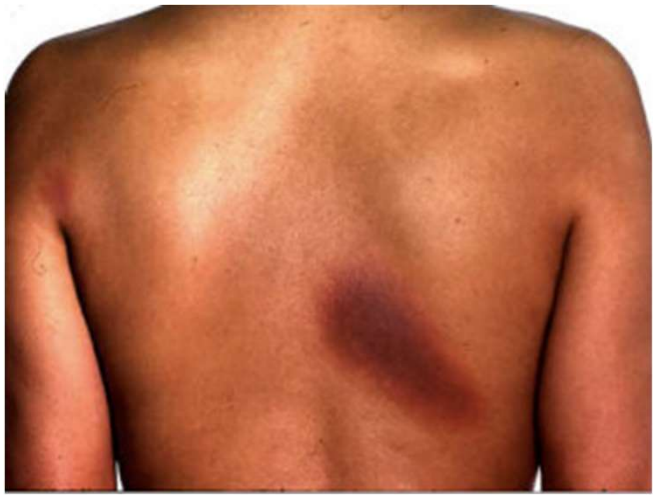
- Stop the drug
- Topical steroids
- Reduce the fever
- Refer to Derm

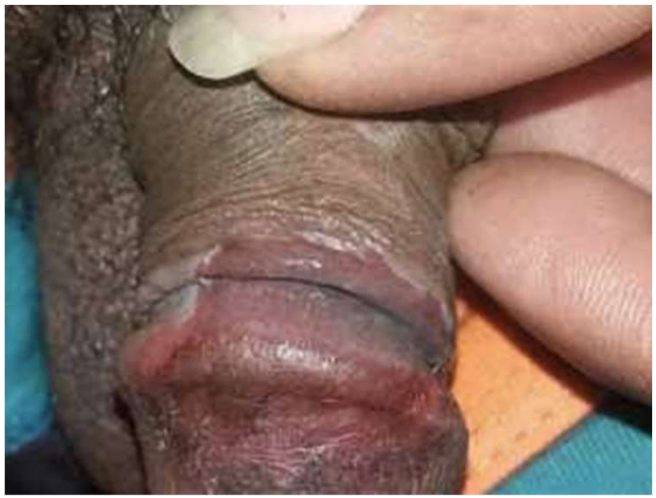


Other Drug Reactions: Non emergent

Fixed Drug Eruptions

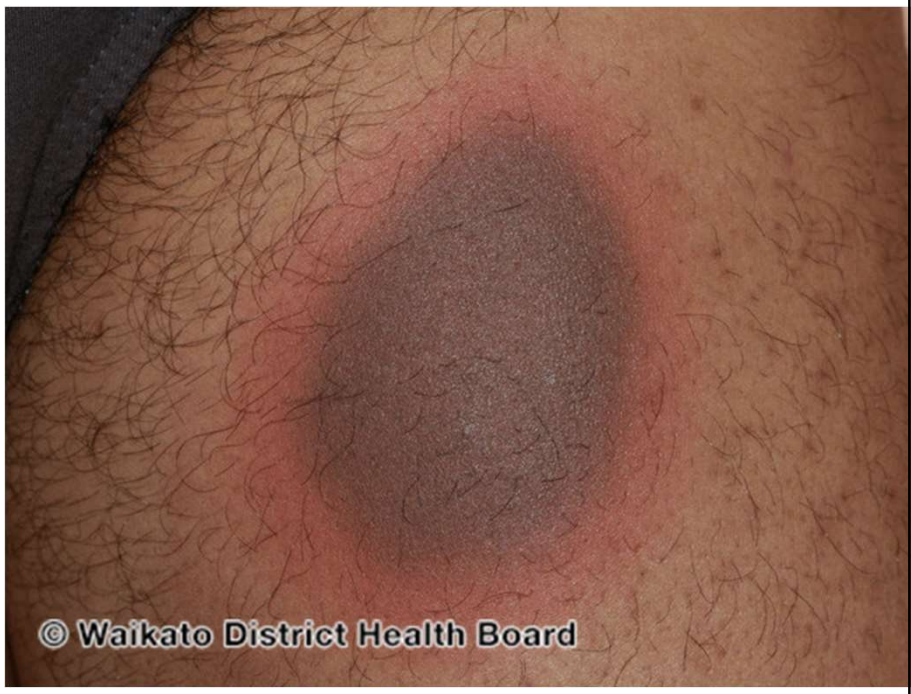
- Onset after initial exposure is 7-14 days
- Then 24-48 hours after reexposure to the drug
- Drug causes: Sulfonamides (Bactrim), NSAIDs, tetracyclines, pseudoephedrine
- Bactrim and tetracyclines are most common cause on the penis





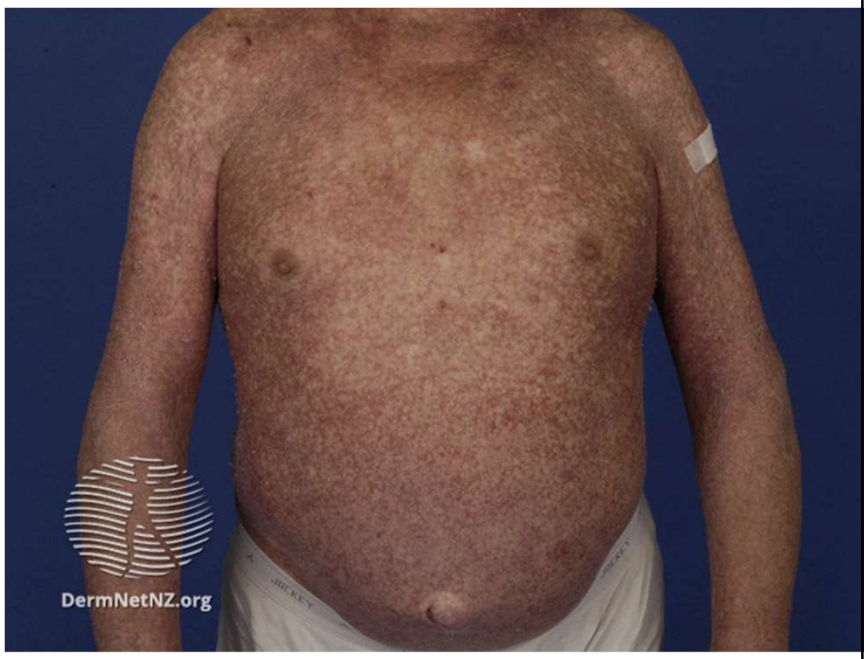
Fixed Drug Eruption Presentation

- One or few dusky to erythematous, possible violaceous smooth plaque. Possibly blistering.
- Locations: Lips, hands, feet, genitals
- Dx: Biopsy or clinical assessment
- DDX: Arthropod bite, EM, Lichen planus
- Treatment: stop the drug, topical steroids

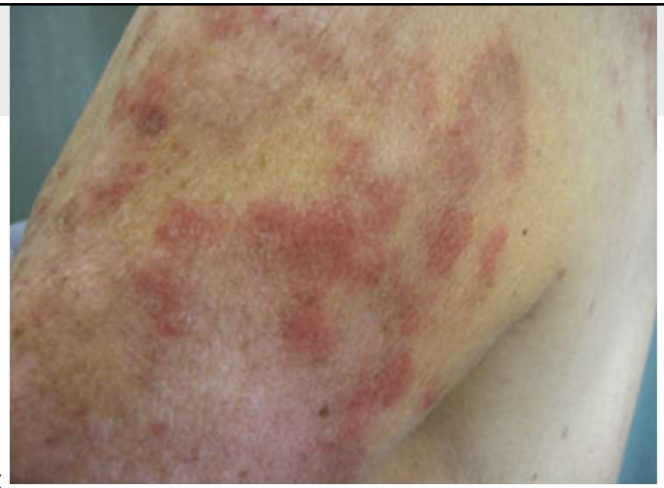


Lichenoid Drug Eruptions

- Mimic lichen planus clinically
- Onset: 3 weeks to 3 years
- Drug causes: Chloroquine, Enalapril (**ACEs/ARBs**), Gold salts, Hydrochlorothiazide, Hydroxychloroquine, Labetalol, Propranolol (**beta blockers**), Methyldopa, Penicillamine, Quinacrine, Quinidine
- Numerous, scattered purple, flat-topped papules
- Biopsy may be helpful to confirm diagnosis
- Treatment: stop the drug, topical steroids.



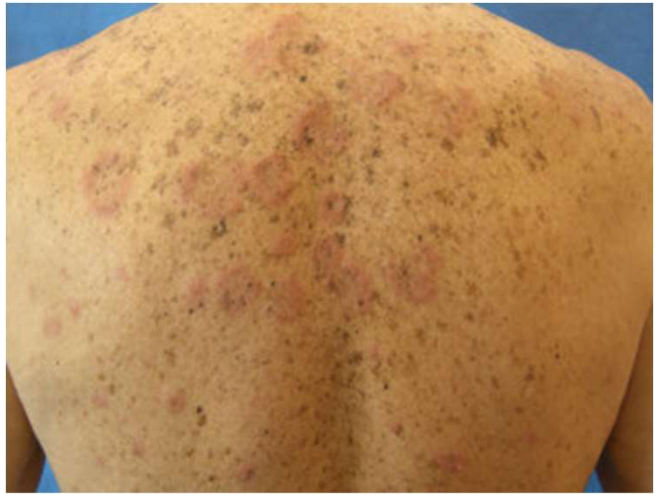
Lupus Erythematosus–Like Drug Eruptions



- F>M
  - >80% of minocycline induced lupus occurs in females
- Most common drugs: hydralazine, procainamide, isoniazid, methyldopa, quinidine, **minocycline**, and chlorpromazine
  - anti–TNF-α (infliximab, etanercept, adalimumab) can occur but rare
- SLE symptoms occur: Arthralgia, myalgia, arthritis, fever, malaise, anorexia, and weight loss
  - Sometime renal or hepatic involvement
- ANA may be positive and remain positive for 6-12 months after discontinuing the drug
- Symptoms resolve 4-6 weeks after stopping the drug
- Cutaneous symptoms are uncommon - rarely see the classic Butterfly rash of SLE

Drug Induced Subacute Lupus Erythematosus

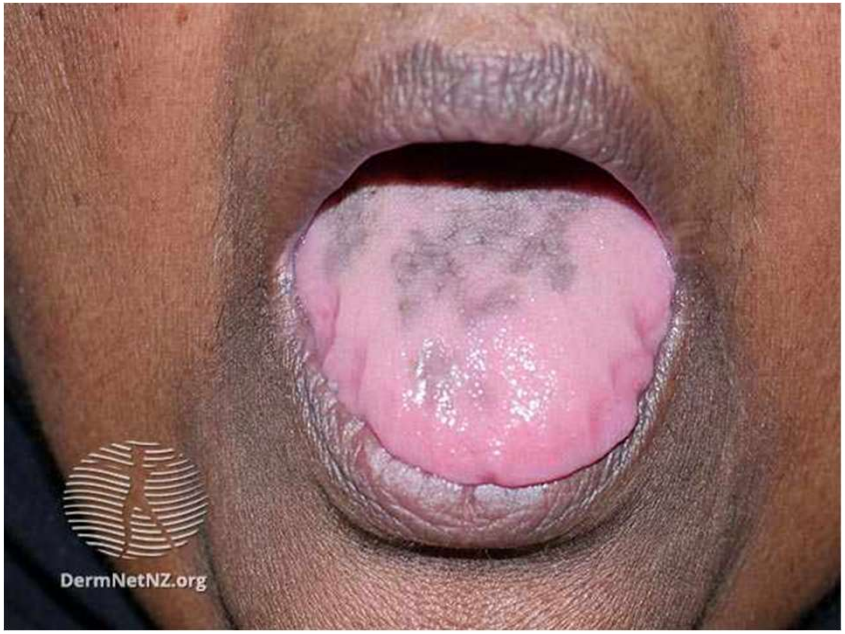
- Onset 2 weeks - 3 years
- Biopsy will not show a difference between SCLE and drug induced form
- Drugs: hydrochlorothiazide, calcium channel blockers, **terbinafine**, NSAIDs, griseofulvin, docetaxel, psoralen plus ultraviolet A (PUVA), and interferon



Pigmentation from Drugs

- Pigmentation can occur with several drugs.
- Most common in derm → Minocycline and hydroxychloroquine

Hydroxychloroquine example →

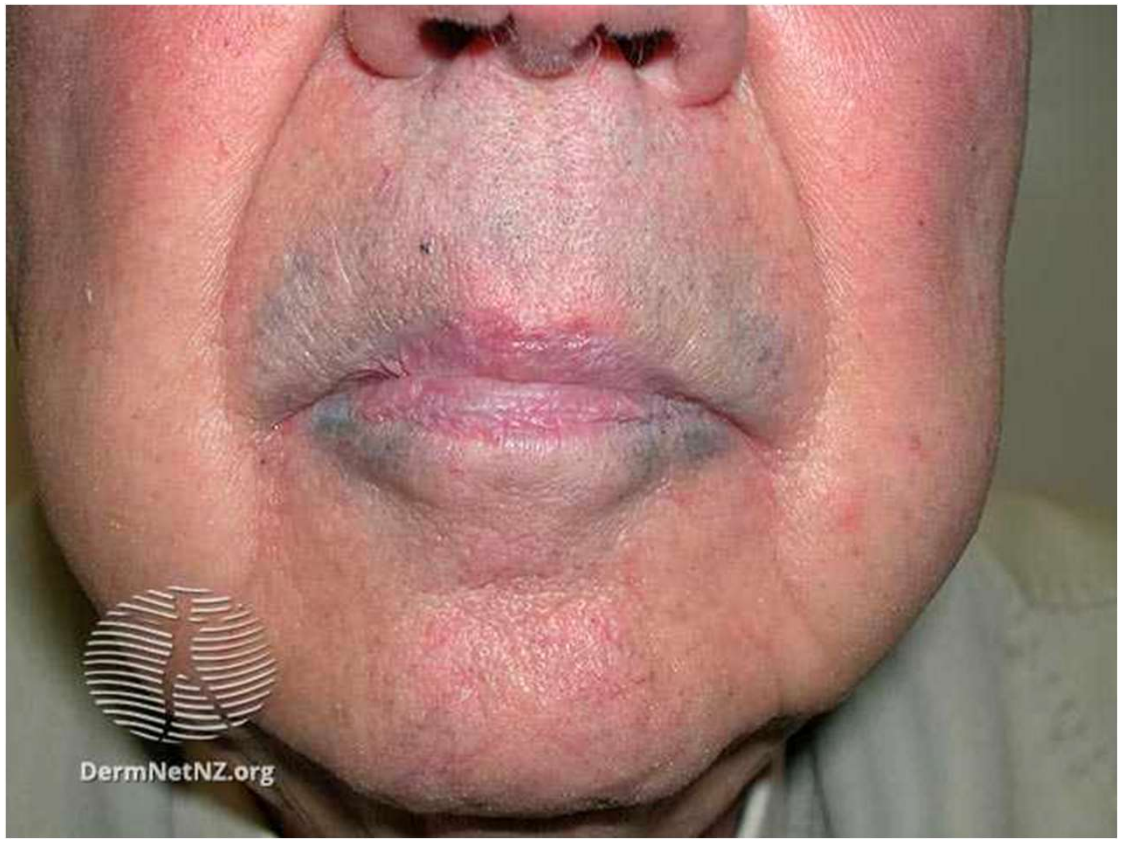


Pigmentation from Drugs

Minocycline induced blueish-grey hyperpigmentation

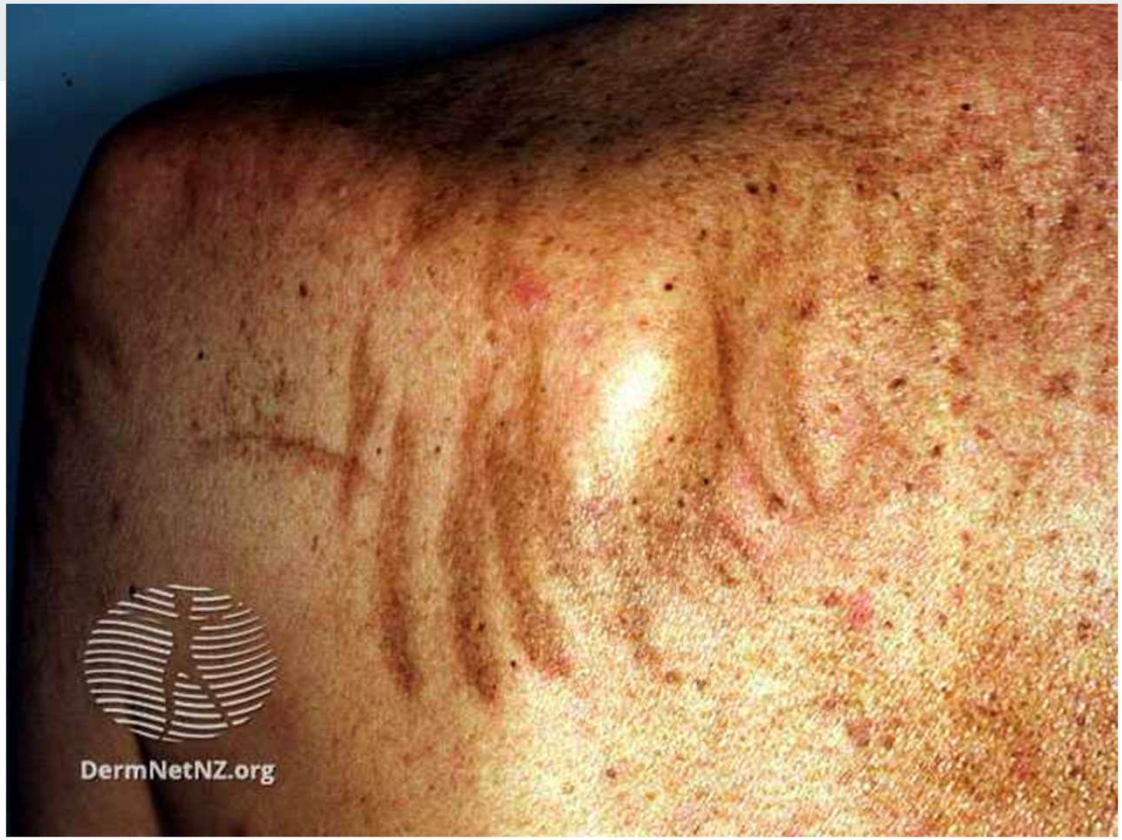
Pigmentation

- Amiodarone - can cause a gray discoloration



Pigmentation

Bleomycin - brownish discoloration in a flagellate formation



Pigmentation - other culprits

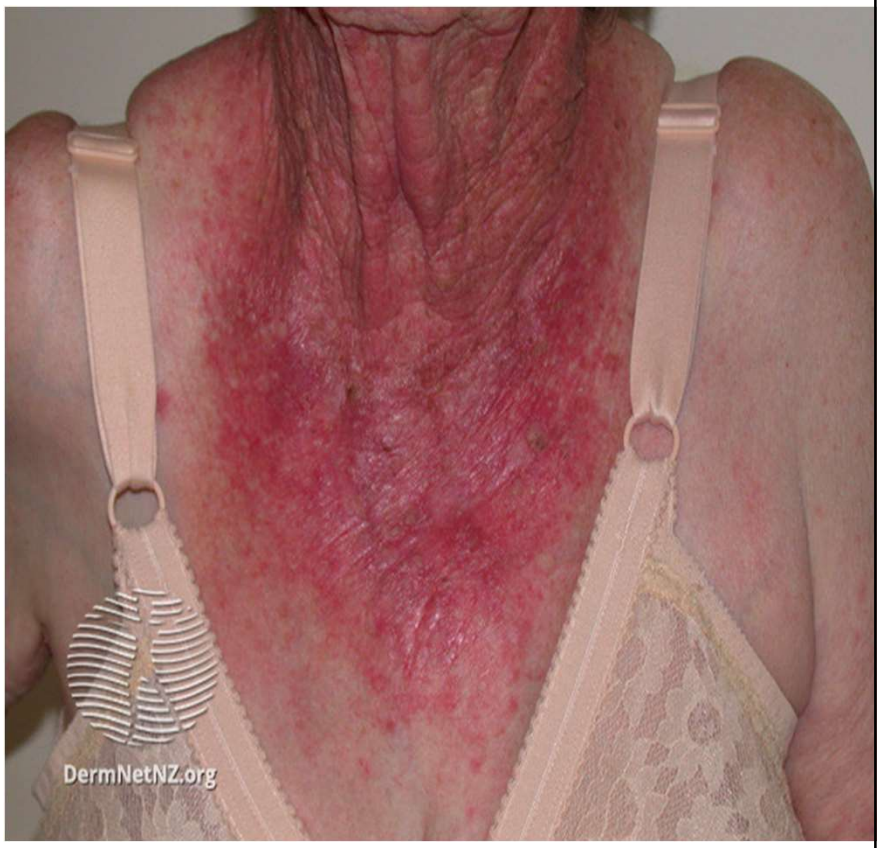
- ACTH - brown discoloration
- Anticancer drugs
- Antimalarials → blue-gray or yellow (Quinacrine)
- Arsenic → diffuse, brown, macular
- Chlorpromazine → gray in sun-exposed areas
- Clofazimine → red
- Heavy metals (silver, gold, bismuth, mercury)
- Methysergide maleate → red
- Psoralens
- Rifampin → red man syndrome

Phototoxicity from Drugs

- Not an allergic response.
- Systemic medications can be a photosensitizer for the skin and cause reactions when the patient has sun exposure.
- Occurs only on sun exposed skin
  - Face, hands, V-formation of chest, etc.
- Can have diffuse erythema or vesicles
- Occurs within minutes or hours of sun exposure while taking the drug

Phototoxicity Drug culprits

- Antibiotics:
  - Tetracyclines (**doxycycline**), Fluoroquinolones, Sulfonamides
- NSAIDs:
  - Ibuprofen, Ketoprofen, Naproxen
- Diuretics:
  - Furosemide, **Hydrochlorothiazide**
- Retinoids:
  - **Isotretinoin**, Acitretin
- DERM Specific Drugs:
  - Photodynamic-therapy (PDT) prophotosensitizers: 5-Aminolevulinic acid, Methyl-5-aminolevulinic acid
  - 5-Fluorouracil (5-FU)



Phototoxicity Drug Culprits cont.

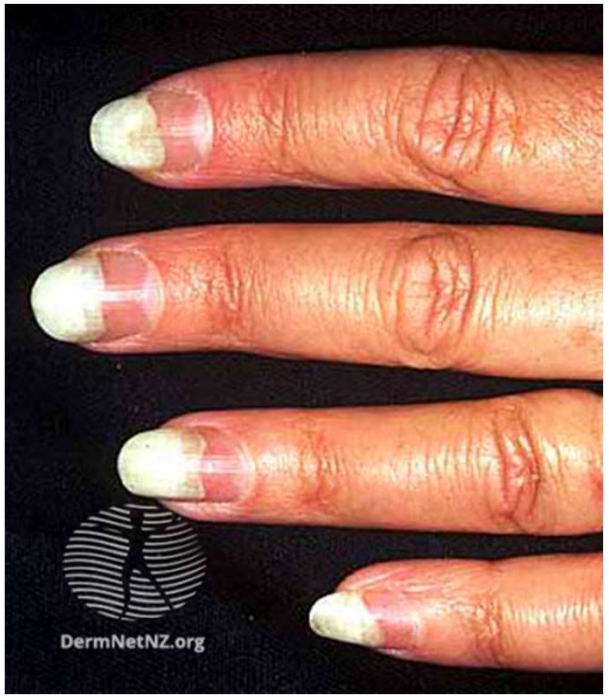
Other Drugs

- Phenothiazines (chlorpromazine, fluphenazine, perazine, perphenazine, thioridazine)
- Thioxanthenes (chlorprothixene, thiothixene)
- Itraconazole
- Voriconazole
- para-Aminobenzoic acid (PABA)
- Amiodarone
- Diltiazem
- Quinidine
- Coal tar

Onycholysis

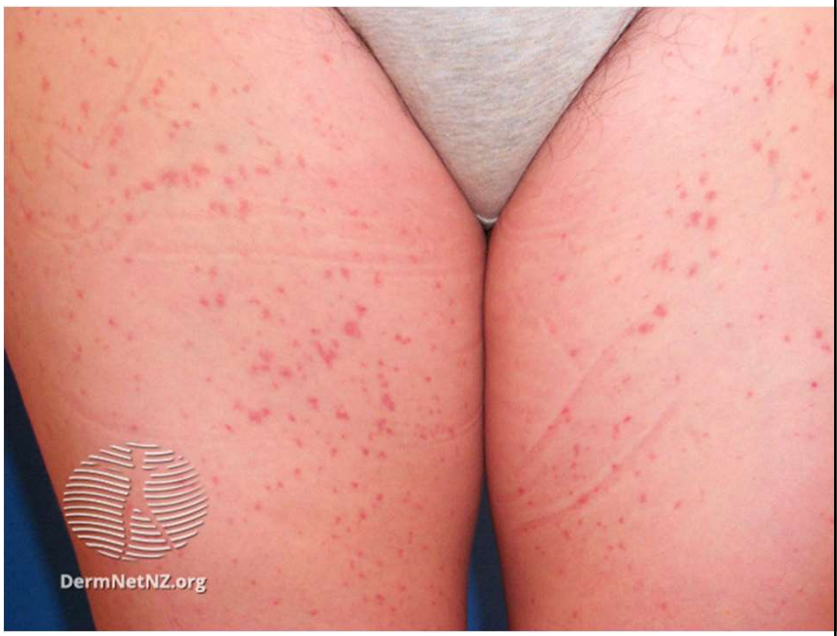
Photosensitivity can cause distal separation of the nail plate from the nail beds

Seen with tetracyclines, psoralens, and fluoroquinolones.



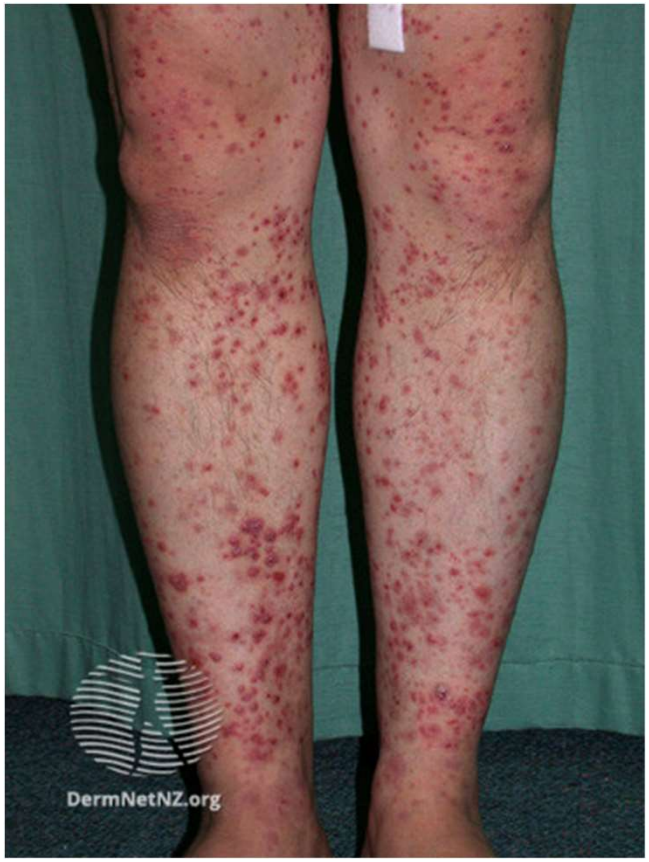
Cutaneous Small Vessel Vasculitis (CSVV)

- Presentation: multiple purpuric, non-blanchable, papule and macules, mainly on the lower legs.
  - Often described as palpable purpura
  - Can also see hemorrhagic vesicles, erythematous wheals (looks like urticaria) or pustules
- Onset: 7-21 days after drug initiation
- Can have systemic symptoms: fever, muscle aches, HA, joint pains, lower extremity edema, peripheral neuropathy, glomerulonephritis

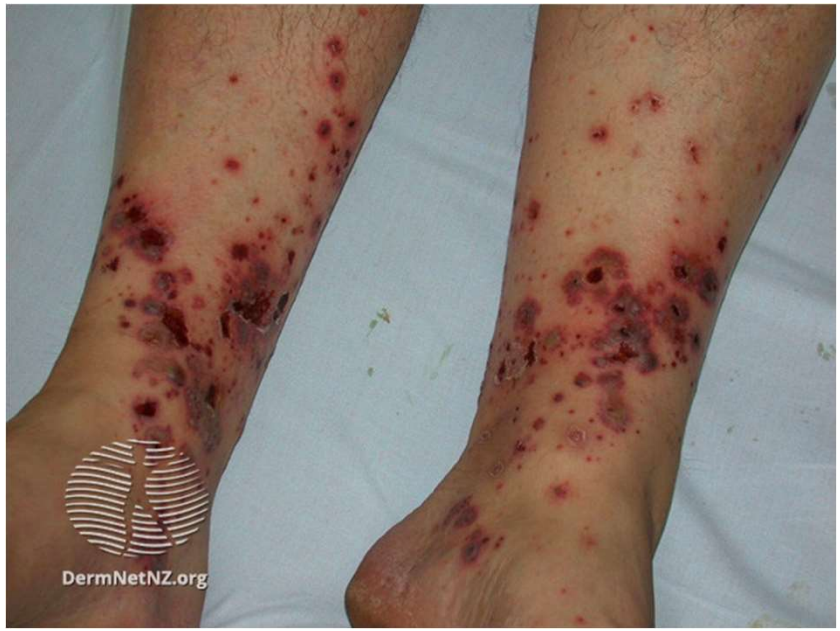


Cutaneous Small Vessel Vasculitis

- Labs: UA, BUN/creatinine to check for renal involvement, possible GI bleeding - occult stool, Skin biopsy may be helpful
- Only 10% of is caused by drugs.
- More often CSVV is caused by infection, autoimmune/connective tissue disease, malignancy or unknown etiology



CSVV Drug Culprits



- PCN
- NSAIDs
- Other antibiotics (cephalosporins, quinolones, sulfa drugs)
- Thiazide diuretics
- Phenytoin
- Allopurinol
- Phenytoin
- Oral anticoagulants, such as warfarin and coumarin
- Systemic immunomodulators (TNF inhibitors)

CSVV Treatment

Mild symptoms:

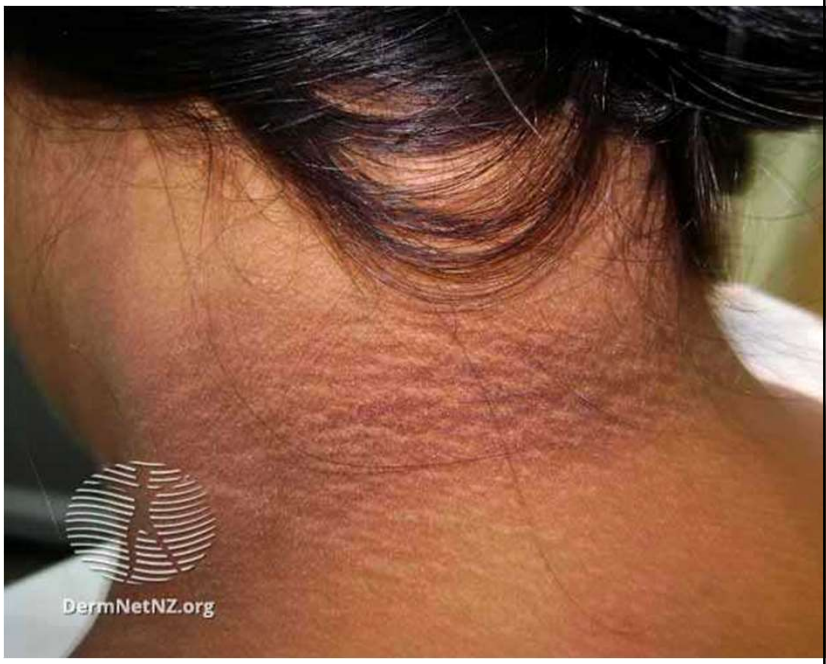
- Monitor and high potency topical steroids
  - Triamcinolone 0.5% ointment, Betamethasone augmented ointment, Clobetasol BID for 2-4 weeks

Severe and/or systemic disease

- Oral steroid taper
- Sometimes need a nonsteroidal immunosuppressive agent (refer to derm)
  - Colchicine or Dapsone
  - Third line agents: hydroxychloroquine, minocycline, methotrexate, mycophenolate, rituximab, IVIG

Acanthosis Nigricans

- Velvety, thickened, hyperpigmented plaques
- Neck, axilla, groin, elbows
- Typically caused by an insulin resistance
- Can be drug induced:
  - nicotinic acid, systemic steroids, estrogen, insulin, niacin, oral contraceptive pills, pituitary extract, triazinate, testosterone, aripiprazole



Warfarin induced skin necrosis

- Onset: 2-5 days after initiation
- Erythematous to violaceous plaques → evolve to hemorrhagic vesicles/bullae and become necrotic ulcers
- Extremely Painful
- More common when initiating high doses of warfarin or if given **without** a heparin transition
  - Locations: breasts, thighs, buttocks (fatty areas)
  - Treatment: Vitamin K, IV heparin, IV protein C concentrate

Test your knowledge

What drugs are the most common causes of most drug eruptions?

A) beta-lactam antibiotics, Sulfonamides, Allopurinol, anti-epileptic drugs, NSAIDS

B) beta-lactam antibiotics, Sulfonamides and tetracyclines

C) beta-lactam antibiotics, Sulfonamides, diuretics and acetaminophen

D) tetracyclines, NSAIDs, beta blockers and oral steroids

Which of the following are correct regarding SJS/TEN?

1. Fever, lymphadenopathy, hepatitis, leukopenia and erosions of the GI and respiratory tracts are common systemic symptoms.
2. SJS involves over 30% body surface area
3. EM, SJS and TEN are the same disease but on a continuum.
4. SJS always starts on the palms

Questions?

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