Cutaneous Drug Reactions

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Faculty/Presenter Disclosure

- **Faculty:** Andrei Metelitsa

- **Relationships with commercial interests:**
  - **Speakers Bureau/Honoraria:** none
  - **Consulting Fees:** none

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  - Dr. Andrei Metelitsa has not received speaking honoraria from the companies

Learning Objectives

- Recognize common pattern of drug eruptions
  - Exanthematous
  - Urticarial
  - Bullous
  - Vasculitis
  - SJS/TEN

Drug Reactions

- Occur in about 2-3% of hospitalized patients
- Of all adverse drug reactions, cutaneous and allergic reactions make up 14%
- Vary in severity (trivial to life threatening)
- Some are expected – others are sporadic

Epidemiology

- Women > men
- Old age
- Immunosupression
- Number of Drugs
- Genetic Predisposition

- Primary drugs in hospitalized patients
  - penicillins, sulfonamides, NSAIDS

Basics of Drug reactions

- Consider drugs (medications, OTC, herbals, etc…) as a potential cause of a skin reaction
- Most drug reactions are inflammatory, generalized, and symmetric (some exceptions – like fixed drug eruption)
- Diagnosis:
  - Apperance
  - Timing
  - Biopsy
  - (Allergy testing is of very limited value – not generally recommended)
- Always document drug reactions in the patient's chart with the medication and description of the reaction

https://www.aad.org/File%20Library/Main%20navigation/.../Drug-Reactions.pdf

Timing

- Immediate reactions
  - < one hour of the last administered dose
  - Example: urticaria, angioedema, anaphylaxis
- Delayed reactions
  - > one hour, but usually > six hours and occasionally weeks to months after the start of administration
  - Example: morbilliform eruptions, fixed drug eruption, SJS, TEN, vasculitis

https://www.aad.org/File%20Library/Main%20navigation/.../Drug-Reactions.pdf

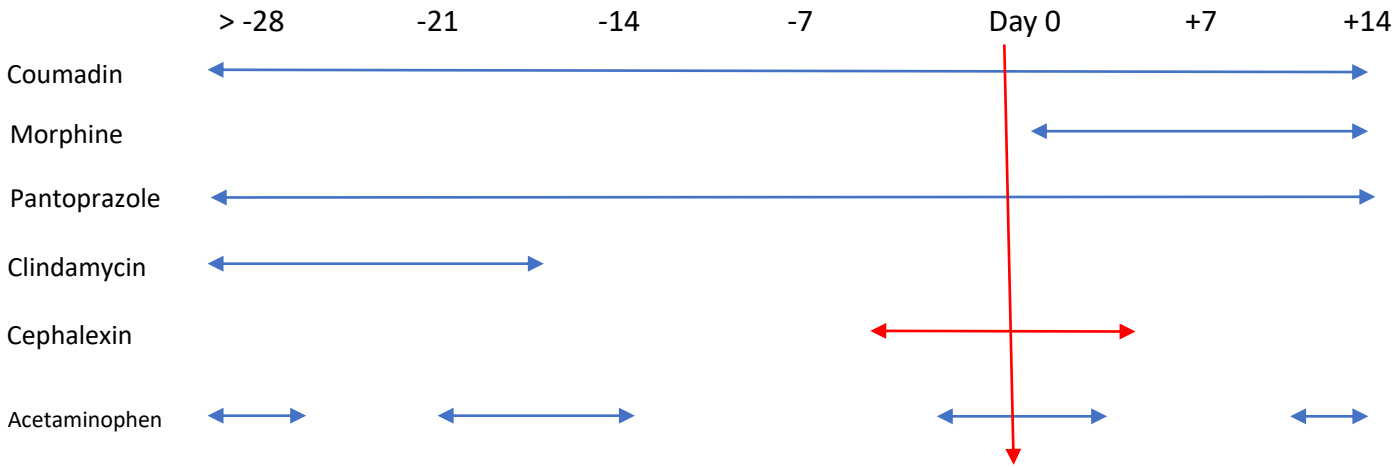
Drug History

- Remember the seven "I's":
  - **I**nstilled (eye drops, ear drops)
  - **I**nhaled (steroids, beta adrenergic)
  - **I**ngested (capsules, tablets, syrup)
  - **I**nserted (suppositories)
  - **I**njected (IM, IV)
  - **I**ncognito (herbs, non- traditional medicine, homeopathic, vitamins, over-the-counter)
  - **I**ntermittent (patients may not reveal medications they take on an intermittent basis unless specifically asked)

https://www.aad.org/File%20Library/Main%20navigation/.../Drug-Reactions.pdf

Drug timeline

- Start with the onset as day 0, and work backwards and forwards



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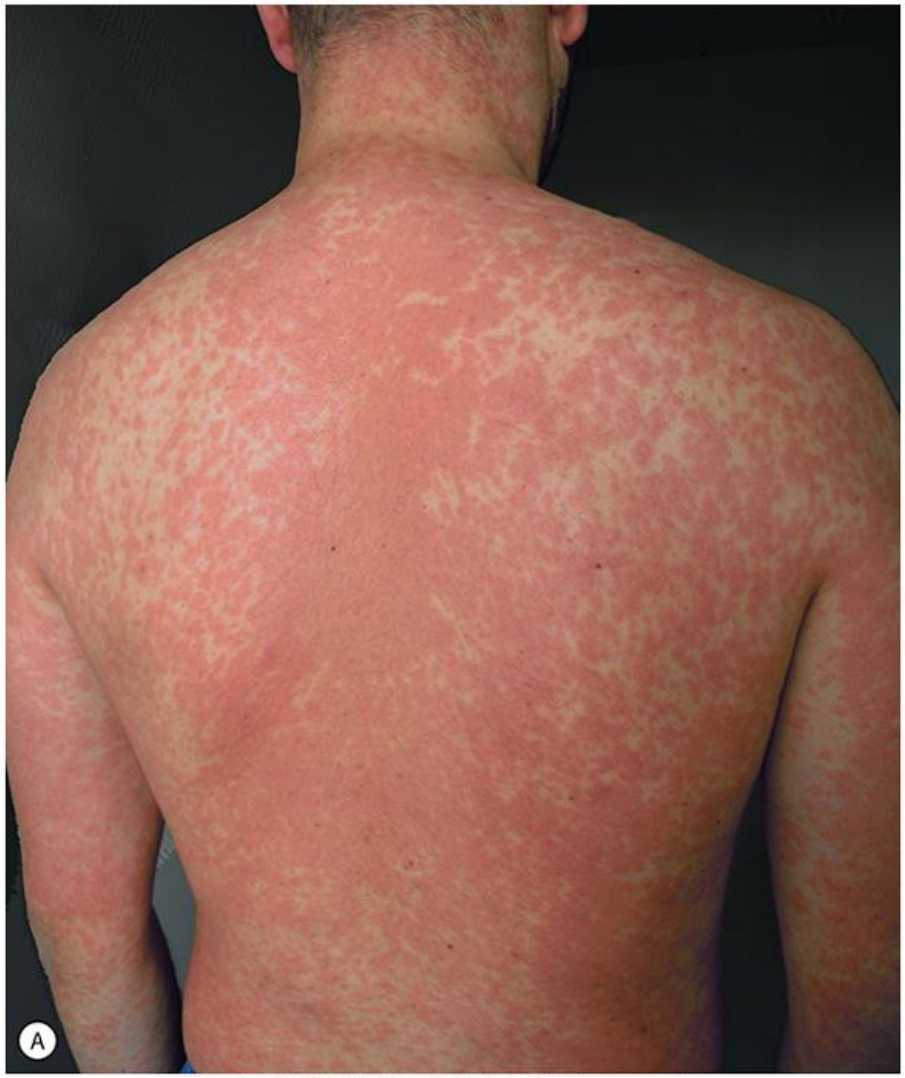
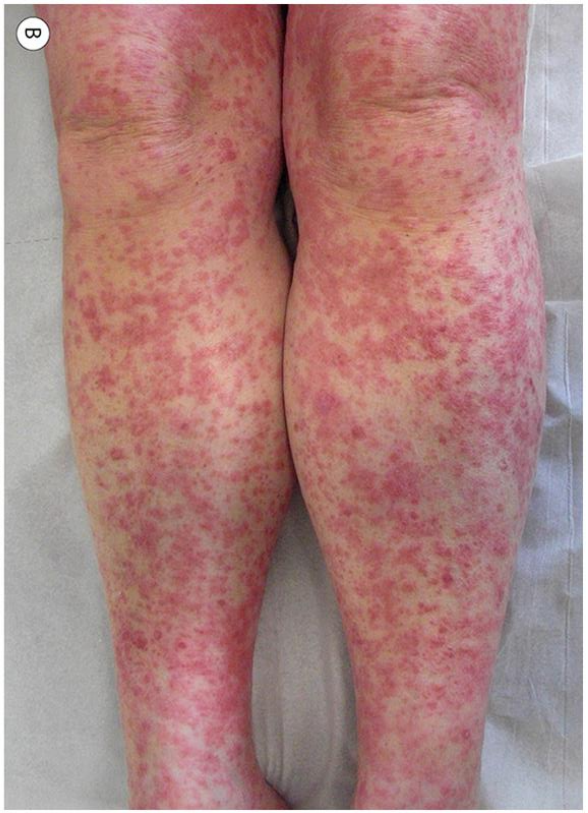
Mechanism of Drug Reactions

- Type 1 IgE dependent drug reactions
  - urticaria, angioedema, anaphylaxis
- Type 2 Cytotoxic drug-induced reactions
  - pemphigus and petechiae
- Type 3 Immune complex
  - Vasculitis, urticarial vasculitis
- Type 4 Delayed Hypersensivity – **most common**
  - exanthem, fixed and lichenoid drug
- Non-immune
  - overdose, drug interactions
- Idiosyncratic
  - DRESS, drug induced lupus

Exanthematous Drug Eruptions





Exanthematous Drug Eruptions

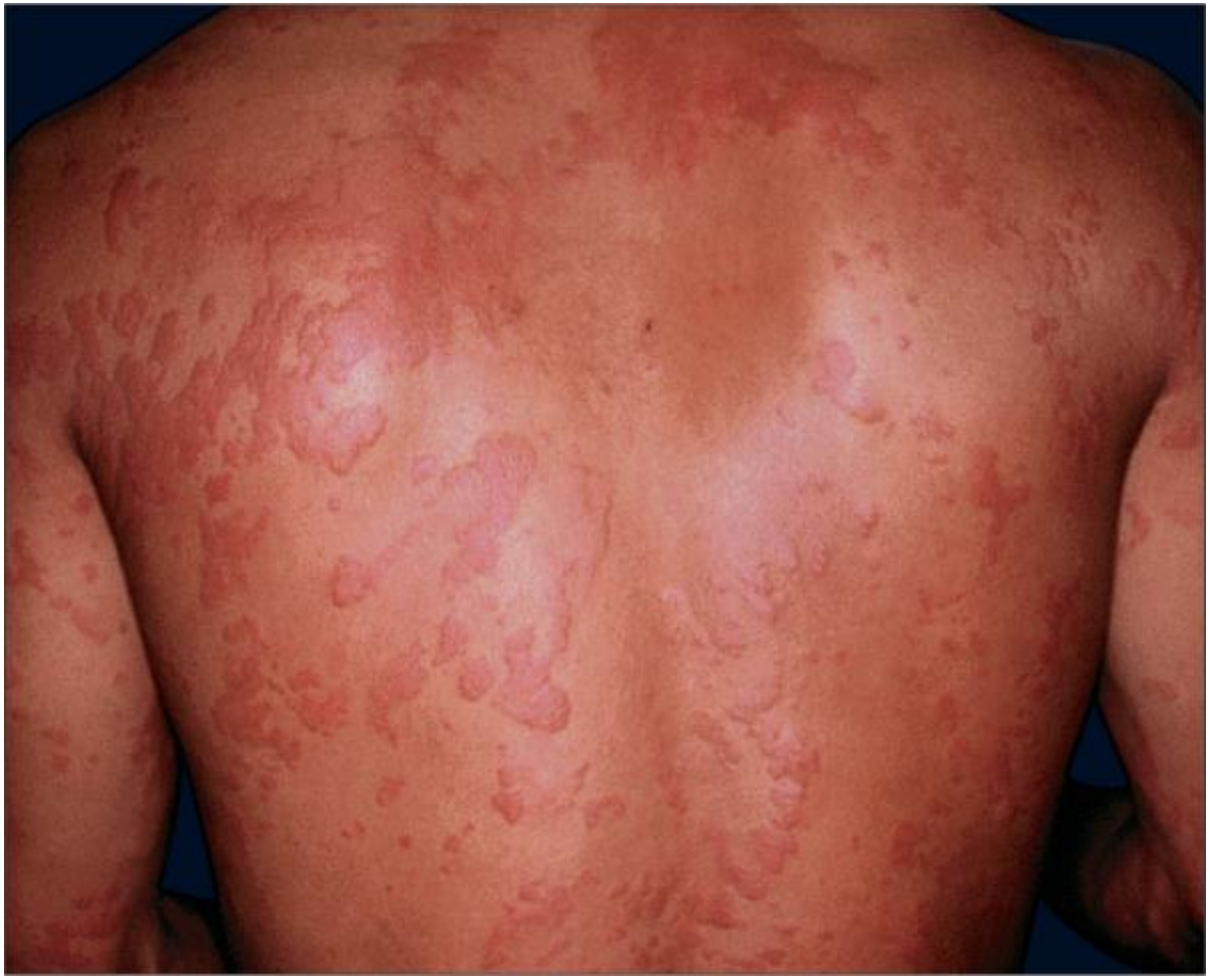
- Most common, type 4 hypersensivity reaction
- "Morbilliform"
- Usually develops 7-14 days after start of new medication
  - Penicillins, sulfonamides, cephalosporins, anticonvulsants
- Begins on trunk and upper extremities -> confluent
  - "maculopapular rash"
- Mucous membranes spared
- Pruritus and low grade fever

Exanthematous Drug Eruptions

- DDx
  - Viral exanthem – very similar, lack of eosinophilia (peds population more common)
  - DRESS – facial edema
  - TEN/SJS – mucous membranes, annular lesions

- Treatment is supportive
  - Stop culprit drug
  - Topical steroids for symptom relief
  - Disappears within 2 weeks without any complications or sequelae

Drug-induced Urticaria



Urticaria to penicillin (Bologna et. al Dermatology)

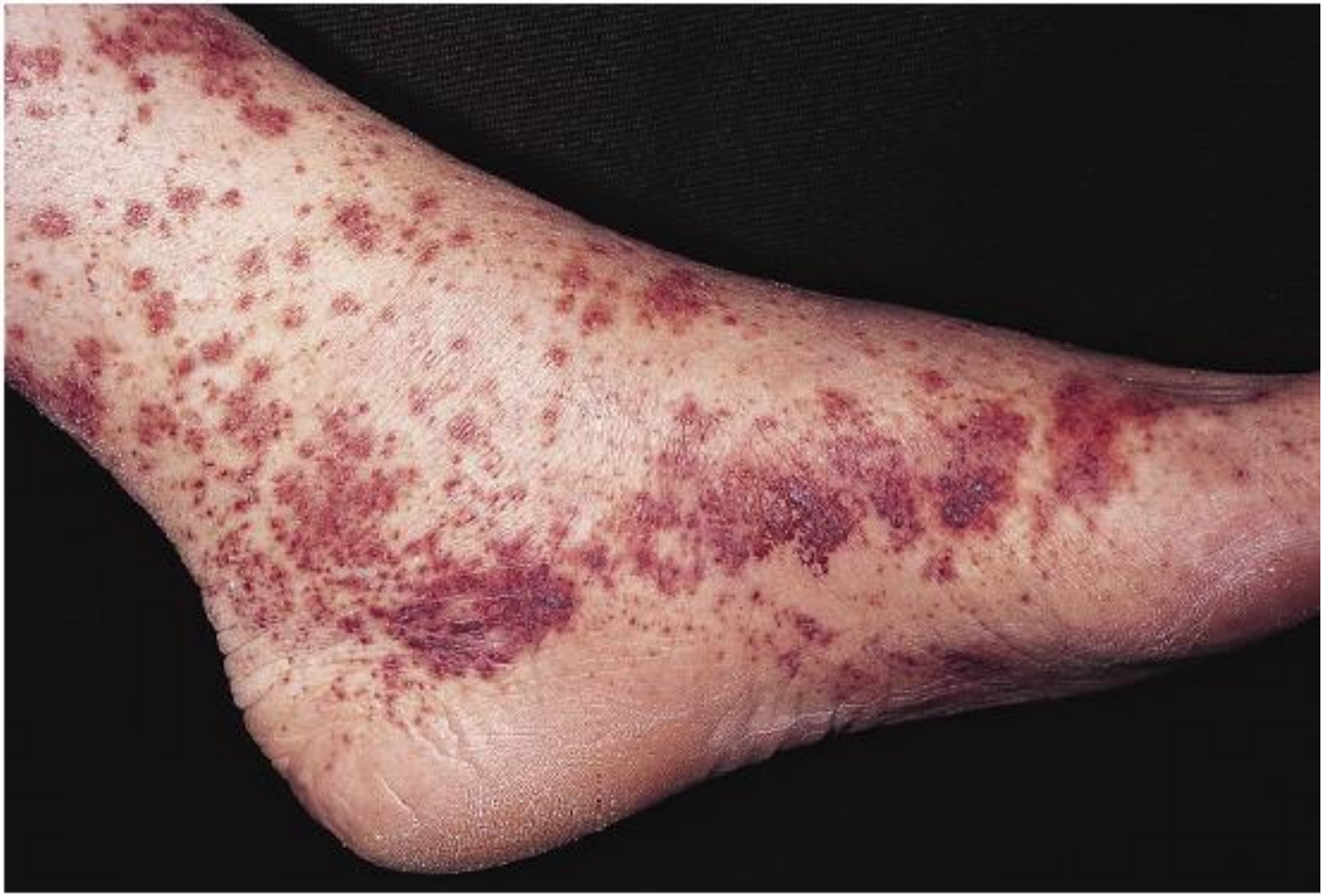
Drug-induced Urticaria

- Type 1 hypersensivity reaction by IgE antibodies
- Erythematous and edematous papules and plaques with pruritus
- Appear within minutes to days of drug administration
  - Antibiotics (penicillins, cephalosporins)
- Duration of lesions less than 24 hrs
  - Urticarial vasculitis more than 24 hrs
  - Acute urticaria <6 weeks
- Angioedema – subcutaneous swelling of the face (eyelids, lips, nose)

Drug-induced Urticaria

- Stop the culprit drug
- Consider antihistamines
  - Newer agent bilastine 20 mg daily (Blexten in Canada)

Vasculitis



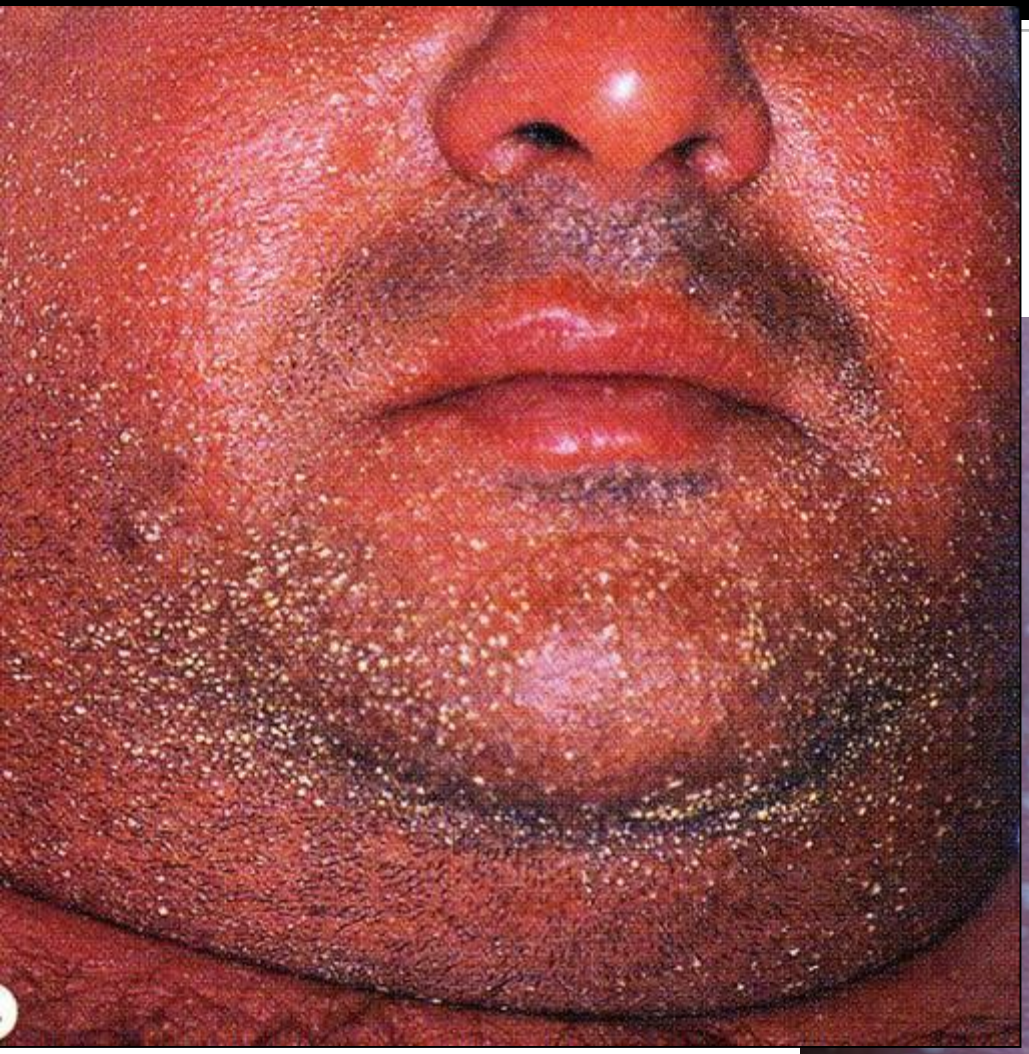
Drug-induced vasculitis

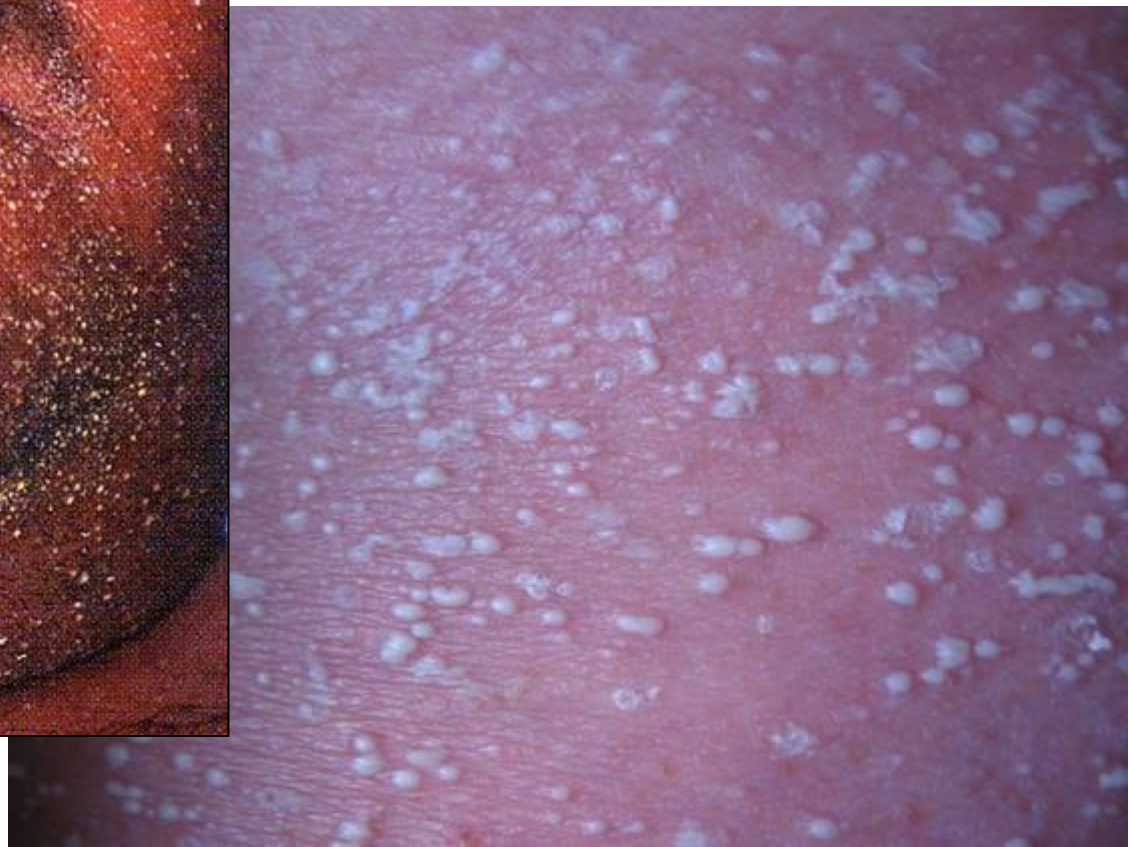
- Small vessel vasculitiis (type 3 reaction)
- Idiopathic, infections (hep C, staph), drugs
- Purpuric papules (non-blancheable), often legs
- Systemic symptoms: fever, myalgia, headache
- Presents within 7 to 21 days of drug administration
- Common drugs: NSAIDS (oral and topical), sulfonamides, cephalosporins,

Drug-induced vasculitis

- Stop culprit drug
- Topical steroids
- Systemic corticosteroids needed if significant systemic involvement
- Rule out Kidney and GI involvement

AGEP

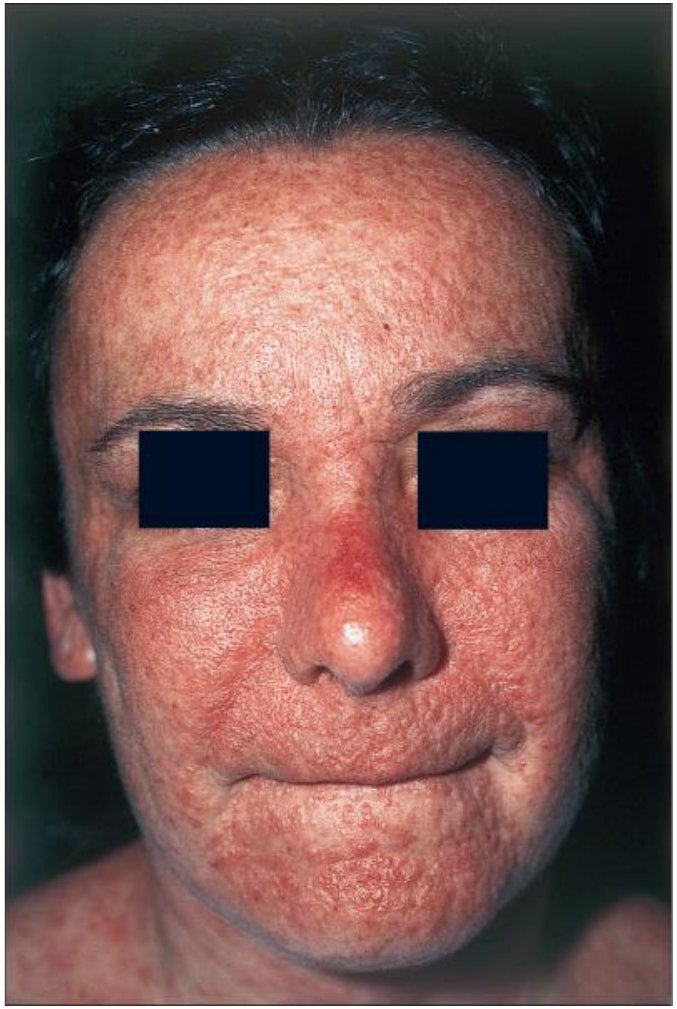




AGEP

- Acute Generalized Exanthematous Pustulosis
- Acute, febrile eruptions with skin lesions
  - numerous small sterile pustules, large erythema
- 90% are drug induced
  - Antibiotics (penicillins, cephalosporins, calcium channel blockers, antimalarials)
- Lesions typically last for 1-2 weeks followed by superficial desquamation
  - Withdraw culprit drug
  - Topical steroids

DRESS



Bologna et. al Dermatology

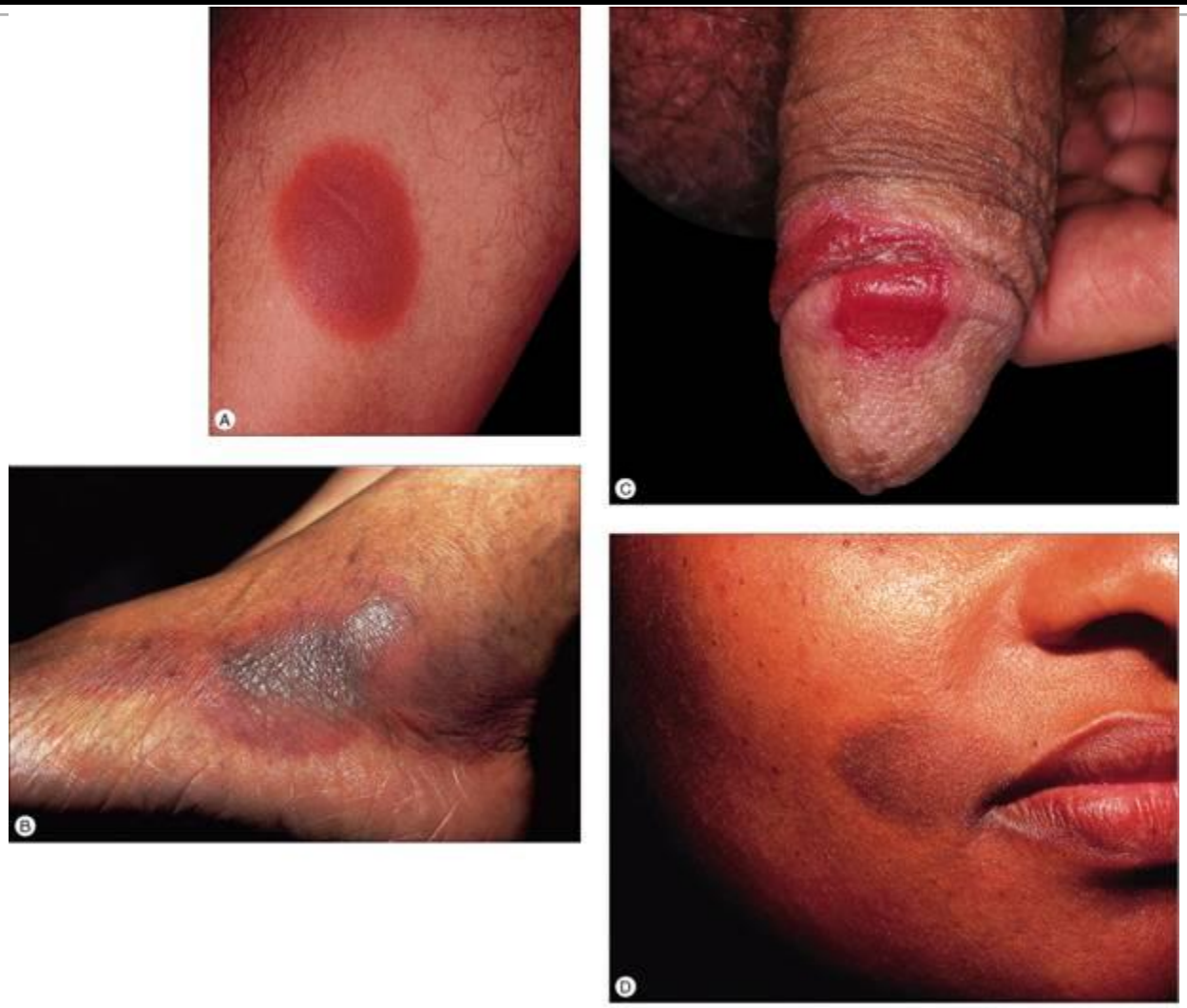
DRESS

- Drug reaction, eosinophilia, systemic symptoms
- Anticonvulsants (phenytoin, carbamazepine, phenobarbital) and sulfonamides
- Develops 2 to 6 weeks after the drug was started
- Edema of the face – hallmark of DRESS
- Fever, exanthem, +/- arthralgia
- Prominent eosinophilia
- Most common organ involved – liver (hepatitis)
  - 10% mortality
  - myocarditis, pneumonitis, nephritis, thyroiditis

DRESS Treatment

- Stop culprit drug
- Mild cases – topical steroids
- More severe cases - systemic corticosteroids
  - Slow taper over several weeks or even months

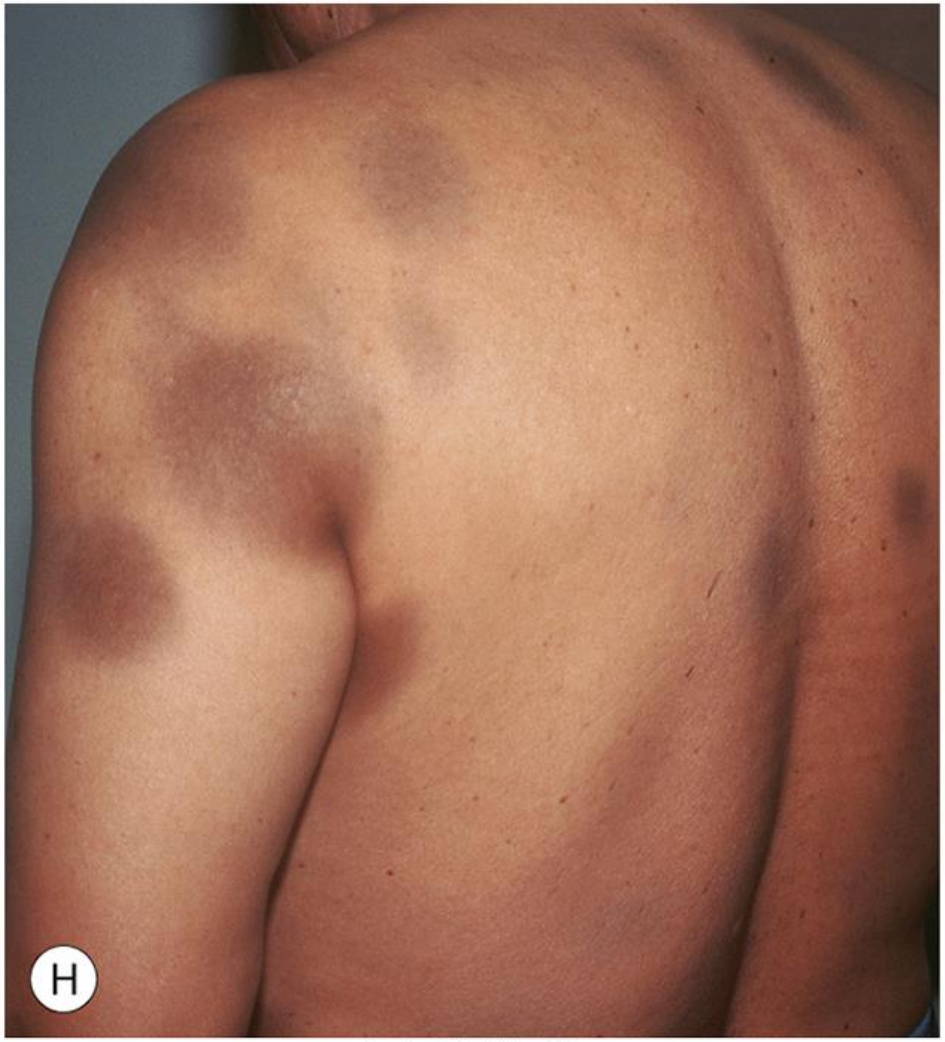
Fixed drug eruption



Fixed drug eruption (FDE)

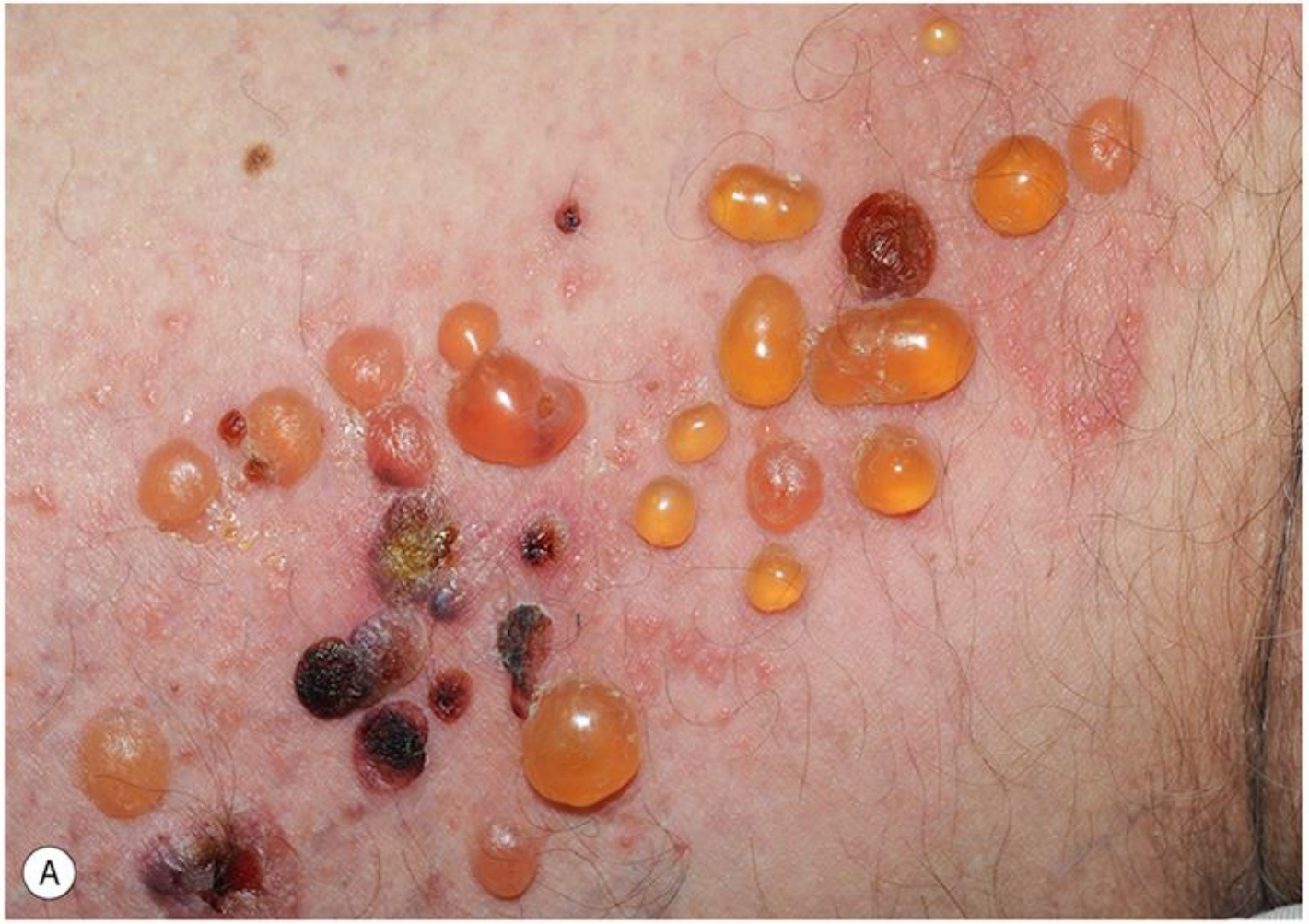
- Peculiar and uncommon type of reaction where single or few skin lesions occur in same (fixed) sites with each administration of drug.
  - They can be oval erythematous or dusky red plaques
  - They can be widespread (generalized fixed drug eruption).
  - There is strong predilection towards genital areas.
  - NSAIDs, sulfa, acetaminophen, etc, are often involved.
  - This is likely a localized type IV hypersensitivity

Fixed Drug Eruption



Courtesy, Mary Stone, MD.

Bullous Pemphigoid

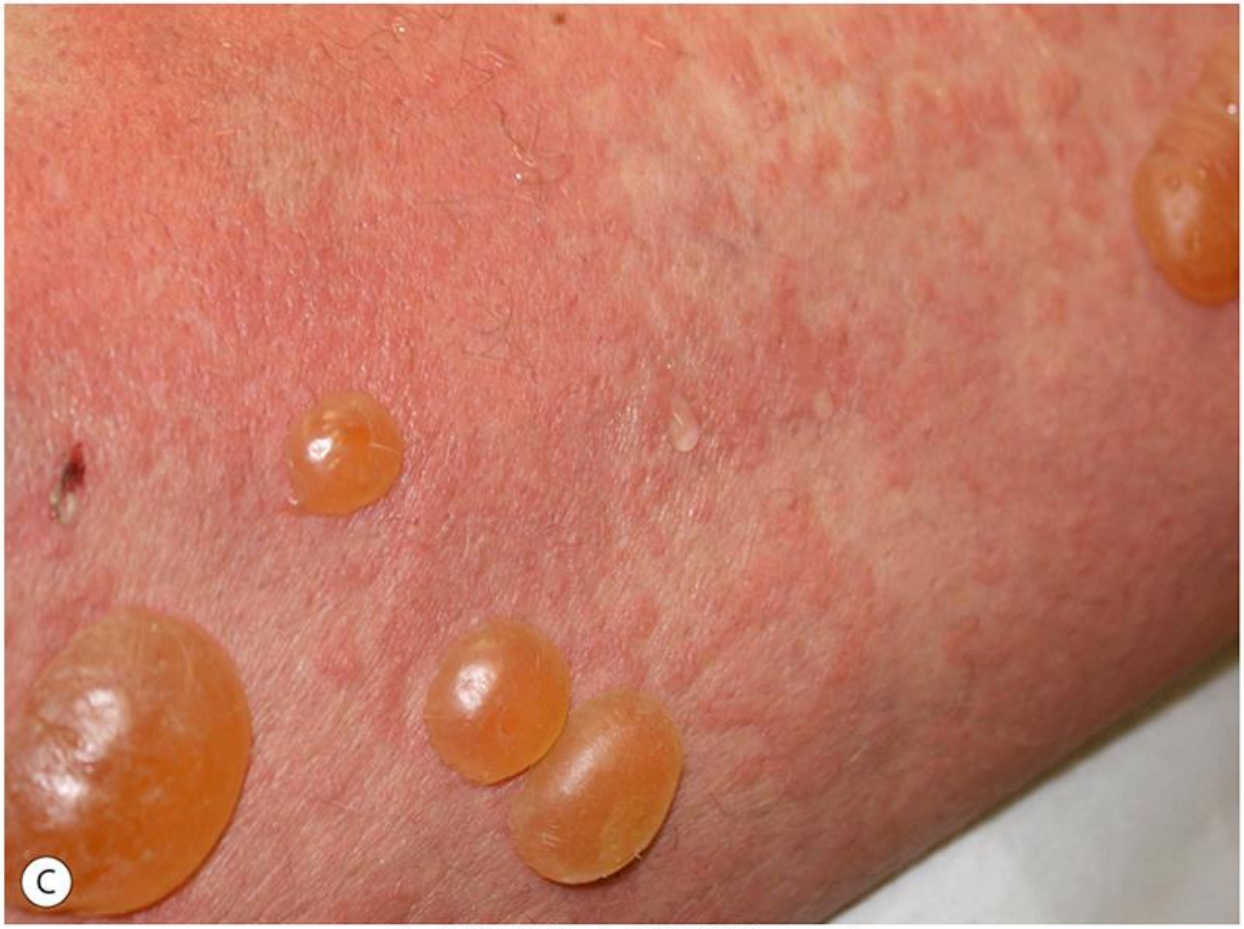


Courtesy, Kalman Watsky, MD.

Bullous Pemphigoid

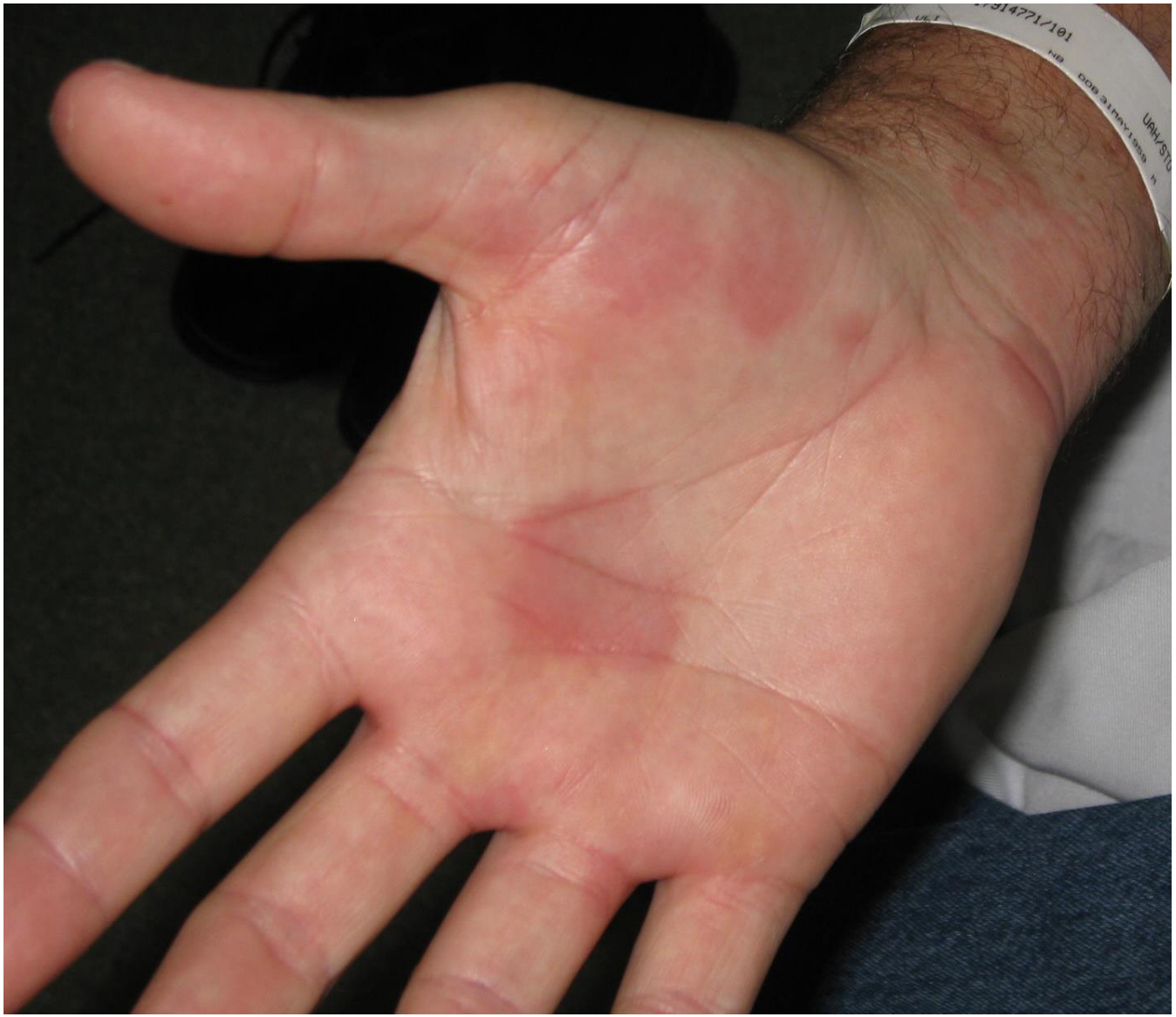
- Most common autoimmune subepidermal blistering disease
- Age over 6o years
- Intensely pruritic eruption
  - Widespread blister formation
- Diuretics (furosemide), NSAIDS, antibioitcs, ACE in
- Intensely pruritic eruption with widespread blister formation
- Tense blisters, contain a clear fluid, and may persist for several days, leaving eroded and crusted areas

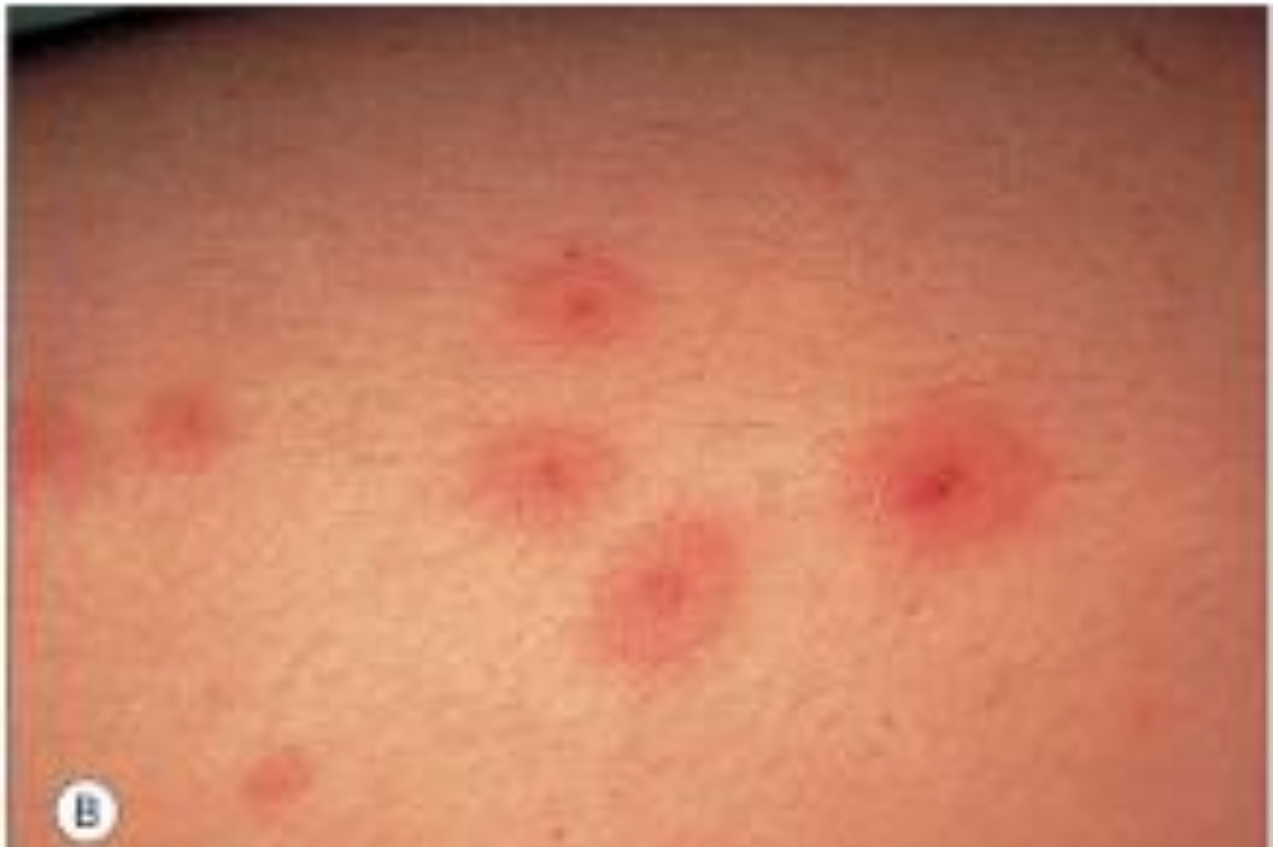
Bullous Pemphigoid



BP Treatment

- Ultrapotent Topical Steroids
- Systemic steroids very slow taper over 6 months! \
  - 0.5-1mg/kg
- Steroid sparing agents
  - Methotrexate, azathioprine, cellcept

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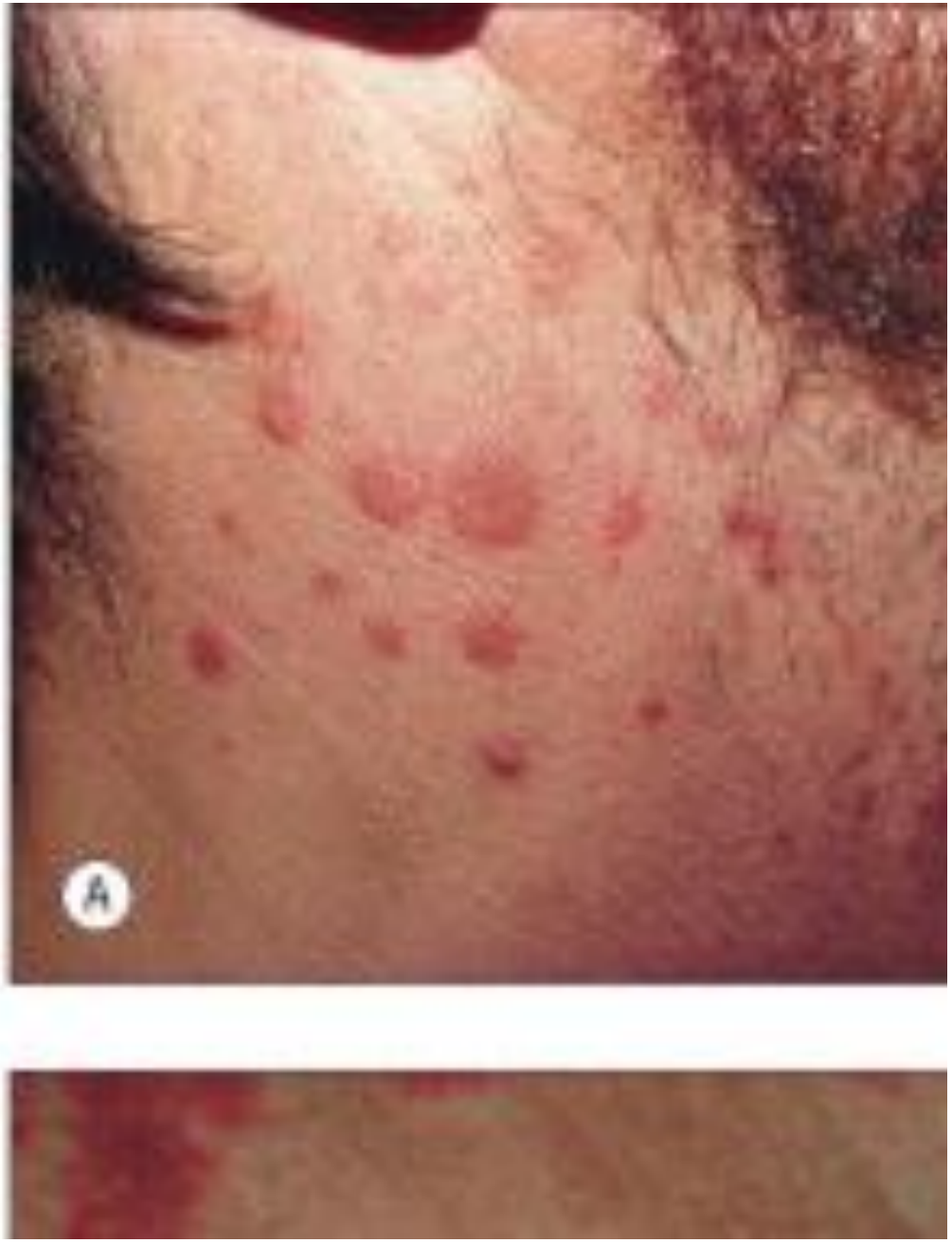
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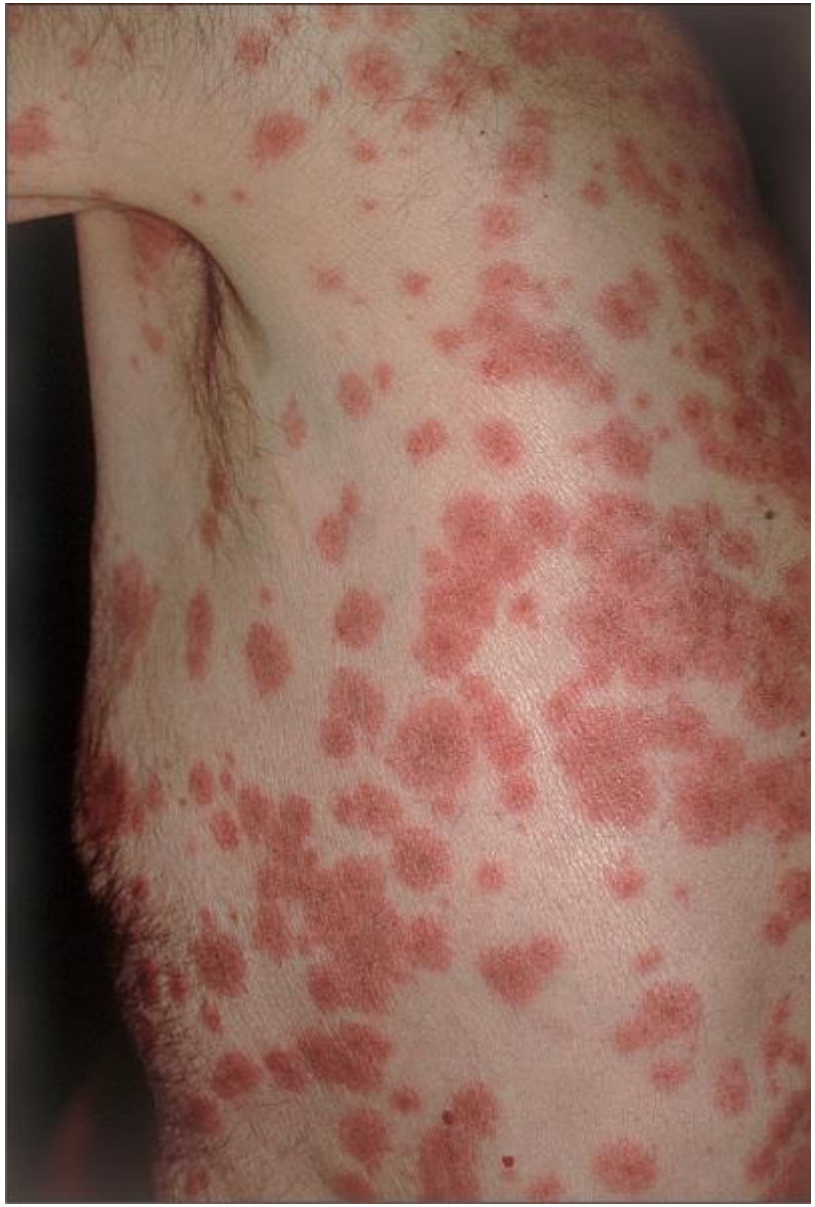
Erythema Multiforme

- A self-limited but potentially recurrent disease
- Abrupt onset of papular 'target' lesions, with the vast majority of lesions appearing within 24 hours
- A preceding HSV infection is the most common precipitating factor; occasionally, there are other preceding infections (Mycoplasma) and drug exposure
- Erythema multiforme does not carry the risk of progressing to toxic epidermal necrolysis

Erythema Multiforme subtypes

- Erythema multiforme minor: typical and/or atypical papular target lesions with LITTLE OR NO mucosal involvement and no systemic symptoms

- Erythema multiforme major: typical and/or occasionally atypical papular target lesions with SEVERE mucosal involvement and systemic features



Natural History

- Almost all of the lesions appearing within 24 hours and full development by 72 hours
- Pruritic or burning sensations within the lesions may be described
- Individual lesions remain fixed at the same site for 7 days or more
- For most individuals with EM, the episode lasts 2 weeks and heals without sequelae

DDx

DIFFERENCES BETWEEN URTICARIA AND ERYTHEMA MULTIFORME	
Urticaria	**Erythema multiforme**
Central zone is normal skin	Central zone is damaged skin (dusky, bullous or crusted)
Lesions are transient, lasting less than 24 hours	Lesions 'fixed' for at least 7 days
New lesions appear daily	All lesions appear within first 72 hours
Associated with swelling of face, hands or feet (angioedema)	No edema

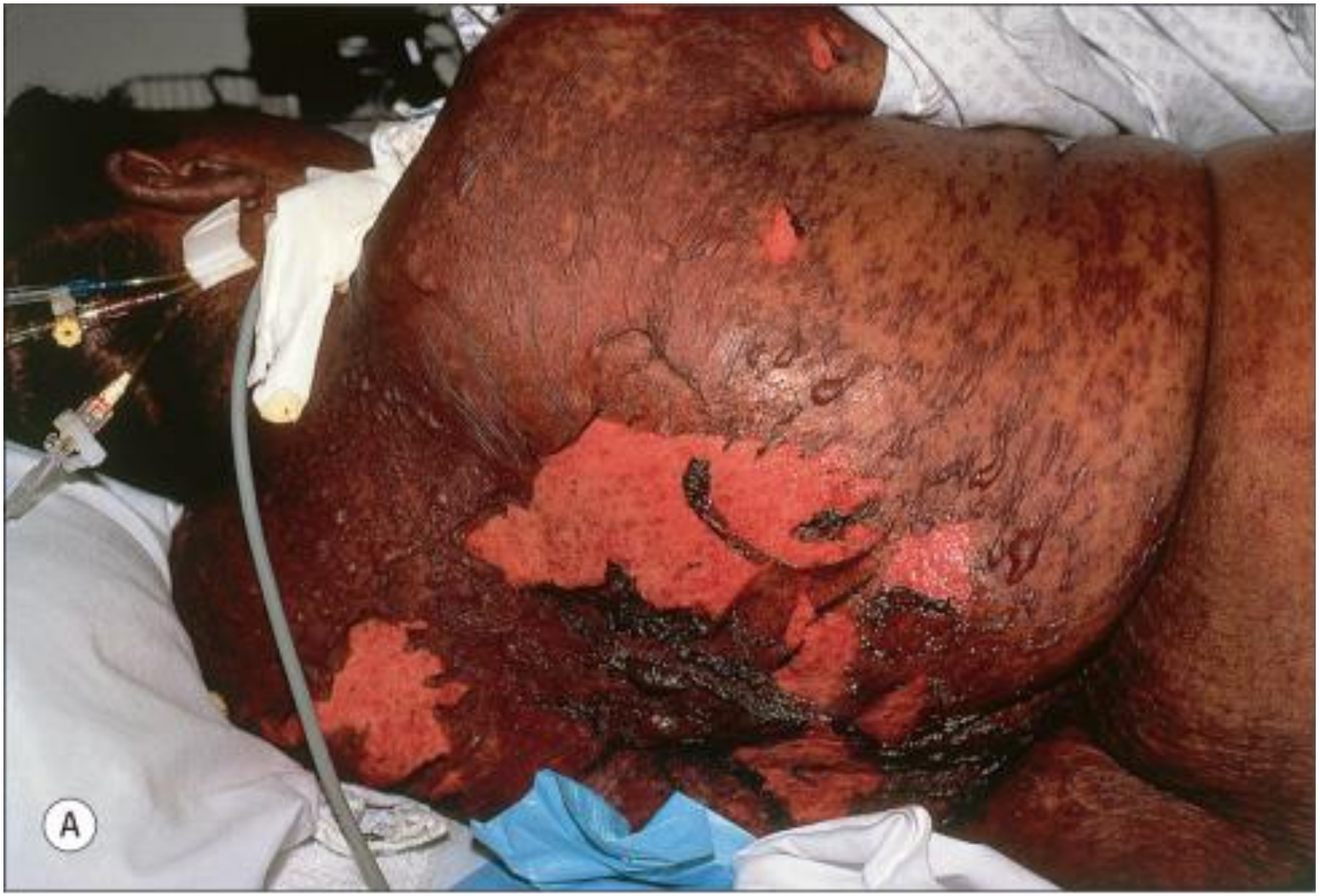
Treatment

- Treat triggers if identified (e.g. HSV or *M. pneumoniae*)
- Oral antihistamines for 3 or 4 days may reduce the stinging and burning of the skin
- Topical corticosteroids
- In severe forms of EM with functional impairment, early therapy with systemic corticosteroids
- Recurrent EM - prophylaxis for at least 6 months with oral valacyclovir

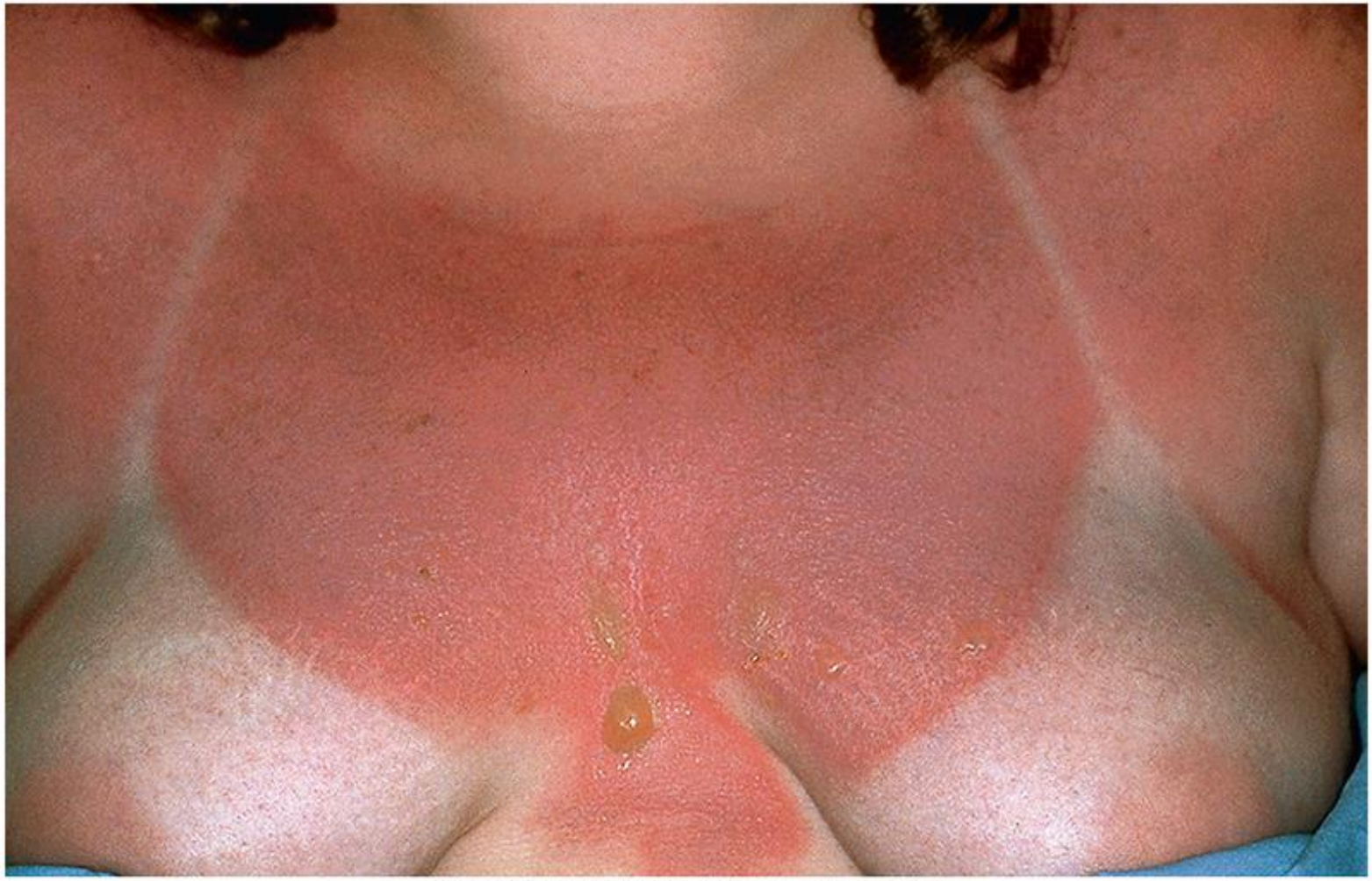
SJS/TEN

- Rare, potentially fatal drug reactions
  - mucocutaneous tenderness and erythema as well as extensive exfoliation
- SJS is characterized by <10% body surface area of epidermal detachment and TEN by >30%
- The medications most frequently incriminated are non-steroidal anti-inflammatory drugs, antibiotics and antiepileptics
- TEN and SJS usually occur 7-21 days after initiation of the responsible drug
- Treatment: consider IVIG

TEN

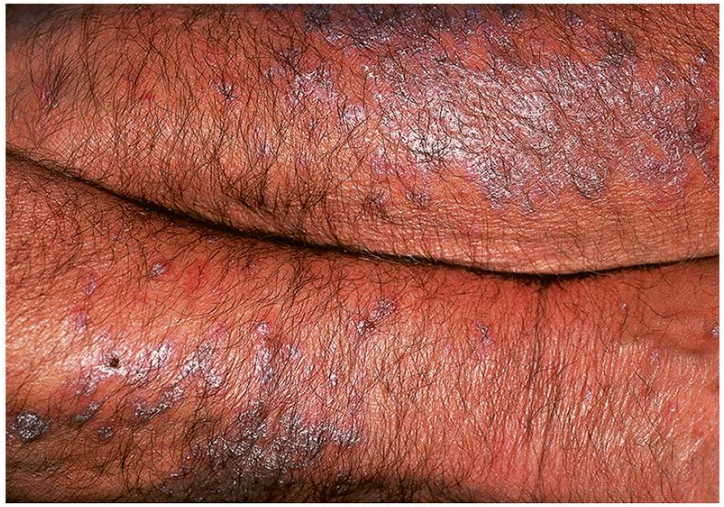


Phototoxic Reactions



Photosensitivity

- **Phototoxic reactions**
  - Exaggerated sunburn, sun-exposed sites
- **Photoallergic reactions**
  - Chronic
  - Both sun-exposed and non-sun exposed



PEARLs

- Exanthematous reaction and urticaria are most common
- DRESS – edema of the face, systemic features
- AGEP – hundreds of sterile pustules
- FDE – recurrent oval plaque, same site
- BP – pruritic, tense blisters in elderly