BIG RED RASH

VIRAL EXANTHEM

vs.

DRUG ERUPTION

Viral Exanthems

- Morbilliform: measles-like: red macules / blotchy redness
- Scarlatiniform: scarlet fever-like: sheets of redness
- Vesicular
- Maculopapular

Viral Exanthem: morbilliform

Terminology

- Morbilliform / Rubeoliform:
- like measles/rubeola (small dark-pink macules in crescentic groups which frequently become confluent)
- like German measles / rubella with papules and macules similar to measles but lighter in color and not arranged in crescentric masses.

- Scarlatiniform: resembling scarlatina / scarlet fever (thickly set red spots)
- Exanthem: the eruption (visible lesion of the skin due to a disease) that characterizes an eruptive fever. A viral exanthem is a rash that arises due to a viral infection.
- Enanthem: an eruption of a mucous surface

Viral Exanthems

- Sudden onset
- Symmetrical
- Widespread including face/palms& soles
- Very common in children
- Asymptomatic to minimal/mild itching
- Patient often not on medications (new/old/OTC's)
- Resolves in 1-2 wks often without any RX

“Non-specific Viral Rash”

- Most viruses produce similar rashes leading to the above term
- Non-specific is the most common viral exanthem and identifying it’s specific viral etiology is most challenging
- Historical elements often aid in the Dx
- season
- exposure history
- local & regional epidemology
- Ex: winter - respiratory viruses
- summer & fall - enteroviruses

Viruses capable of causing non-specific viral exanthems

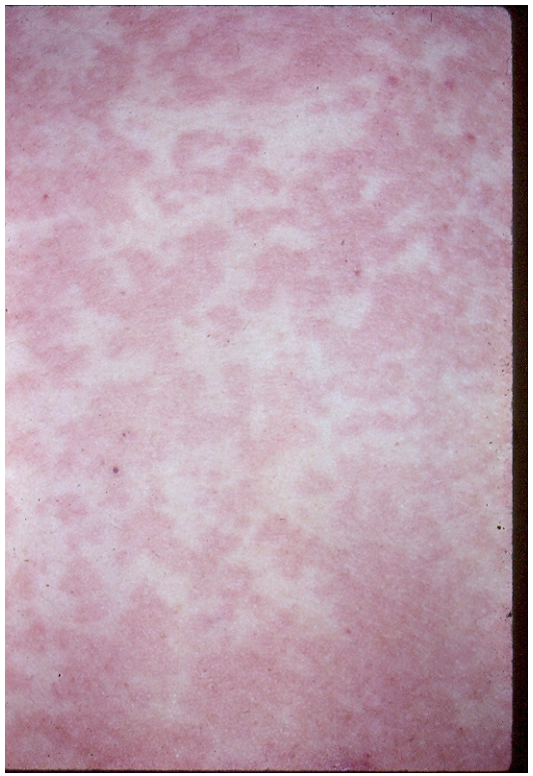
- Non-polio enteroviruses- enterovirus
- Coxsackie virus
- echovirus
- Epstein-Barr virus
- Human herpesvirus-6
- Human herpesvirus-7
- Parvovirus B19

Cont.

- Respiratory viruses:
- rhinovirus
- adenovirus
- parainfluenza virus
- respiratory syncytial virus
- influenza virus

Epstein-Barr Virus

Mono rash: morbilliform



Measles- macules & papules

Measles- macules & papules

Measles- note conjunctivitis

Measles- associated conjunctivitis

German Measles: macules & papules in confluence

German Measles: lymphadenopathy

Morbilliform Rash

- MEASLES / RUBEOLA
- begins on face & progresses downward
- macules & papules, discrete than confluent & diffuse
- cough, corzya & conjunctivitis
- Koplik's spots: blue-white,vesiculo-erosive on an erythematous base of mm (appear BEFORE the exanthem develops)
- GERMAN MEASLES / RUBELLA
- associated with posterior cervical adenopathy

Scarlatiniform Rash

- SCARLATINA / SCARLET FEVER
- scarlet eruption of thickly/closely set red spots (‘sheets of redness’)
- chills, fever, vomiting & pharyngitis
- strawberry tongue
- due to specific strains of hemolytic streptococcus (S. scarlatinae)
- kidney complication: nephritis

Fifth Disease : macules & papules in confluence

Fifth Disease : macules & papules

Fifth Disease / Erythema Infectiosum

- “Slapped cheek” syndrome
- Parvovirus B19
- Community outbreaks (winter & spring)
- 30% susceptible adults acquire infection
- Usually assymptomatic
- 10% prodromal symptoms- pruritus, low-grade fever, malaise, sore throat
- Lymphadenopathy absent
- Arthritis small joints esp. females

Fifth Disease

- Facial erythema-slapped cheek look
- 2 days lacy erythema in a ‘fish-net’ pattern begins on proximal extremities and extends to trunk & bottocks in 6-14 days
- Eruption can fade & reappear for 2-3 wks

Parvovirus B19 & pregnancy

- 60% pregnant women immune to the virus
- Only 30-44% report signs (arthralgias & rash)of acute infection during pregnancy
- 8-10% overall risk of fetal loss / greatest when infection <20 weeks gestation
- Affected fetus: anemia, high output cardiac failure, pleural effusion, polyhydramnios, & non-immune hydrops fetalis

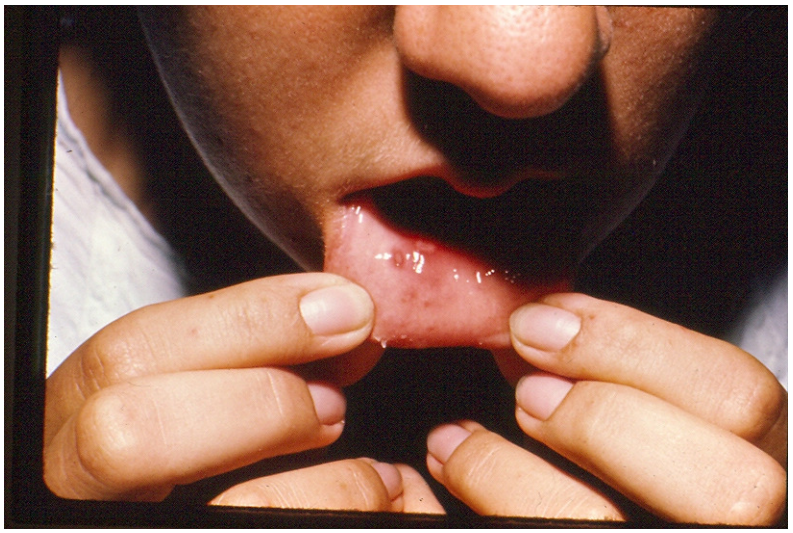
Hand, Foot, and Mouth Disease

- Highly contagious viral infection that causes aphthae-like oral erosions & a vesicular eruption on the hands and feet
- Classically benign and self limited
- Coxsackie A 16 virus
- Can be due to enterovirus 71 and may have associated neurological syndromes (aseptic meningitis ,G-B Syndrome, acute transverse myelitis, polio-like syndrome, etc)

Hand Foot & Mouth Disease

H F & M Disease

H F & M Disease
(can be painful, esp in children)



HFM : hard palate lesions (papules & vesicles)

Rx HF&M Disease

- Nothing: self limited
- Children may be isolated for 3-7 days
- Acyclovir suspension in children if symptomatic

Non-skin findings in these non-specific viral exanthems may help

- Fever
- Constitutional symptoms

History & Physical Exam

- Chief Complaint: brief/patients own words
- Present Illness : chronological order of each symptom (time and mode of onset, duration and severity). Rx if any.
- Past Illnesses: esp. past infectious diseases and allergies/drug sensitivities
- Personal History: esp. medications (including OTC's) /occupational and environmental (including travel)
- Family Hx: including allergies
- Review of Systems

Physical Examination

- VITAL SIGNS: weight, height, PULSE, TEMPERATURE, RESPIRATION, and BLOOD PRESSURE.
- HOW SICK DOSE THIS PATIENT LOOK
- SKIN & MUCOUS MEMBRANES

Non-polio enteroviruses

- Fever
- Abdominal pain & vomiting
- Multi organ involvement:
- central nervous system
- pulmonary system
- cardiac system
- Can occasionally produce a petechial rash that mimics meningococcemia

Epstein-Barr virus

- Fever
- Sore throat / pharyngitis
- Lymphadenopathy
- Periorbital edema
- Abdominal pain
- Myalgias
- Hepatosplenomegaly
- Ocassionally vesicular, urticarial or petechical rash

- Laboratory work as indicated by Hx & P.Ex
- Skin Biopsy: non-specific but may help to differentiate from SSSS & drug hypersentivity reactions

Drug Eruptions

- Sudden onset
- Symmertrical
- Widespread : espically torso/occasionally extremities/rare face and palms&soles
- Common in adults especially with aging and polypharmacy (new/old & OTC's)
- Symptomatic with mild to severe itching
- Generally need to withdraw causative agent

What is a drug?

- Prescribed medications:
- ingested
- inhaled
- injected
- applied to skin or mucous membranes
  - (oral, rectal, occular)
- OTC ‘medications” including vitamins, supplements, etc.

How common are Cutaneous Adverse Drug Events?

- 2.26 CADE's per 1000 people seek medical attention in a national ambulatory medical care survey done over 10 years.
- Average medications were 2.2, increased with age (peak 70-79 yo), often antimicrobials, Dx: dermatitis, urticaria
- 3-6%of all hospital admissions due to CADE
- 2-3% of hospitalized patients develop a CADE
- 3-5 / 100 patients have CADE to aminopenicillins and sulfonamides

- A drug reaction or SCAR (severe cutaneous adverse reaction) is NOT RARE to the patient who has it and the physician who has to treat it!!!!!

Drugs cause a wide spectrum of Cutaneous Reaction

- Maculopapular (exanthematous) eruptions
- Anaphylactic reactions
- Serum sickness
- Acneiform (pustular) eruptions
- Alopecia
- Erythema nodosum
- Exfoliative erythroderma
- Fixed drug eruptions
- Lichen planus-like eruptions
- Erythema multiforme-like eruptions

Cutaneous Reactions cont.

- Lupus-like eruptions
- Photosentivity
- Skin pigmentation disorders
- Pityriasis rosea-like eruptions
- Toxic epidermal necrolysis
- Small-vessel cutaneous vasculitis
- Vesicles and blisters
- Ocular pemphigoid
- Chemotherapy-induced acral erythema

4 Key Steps in Evaluating a Drug Rash

- 1. Is it a drug rash?
- 2. Is it cutaneous only or a systemic reaction to a drug?
- How should it be managed?
- Are diagnostic tests necessary, and if so, which?
- 3.Which drug is the offending agent?
- 4. Is it safe to re-challenge the patient with the offending agent?

Essential

- Prompt identification & discontinuance of the offending agent
- If on multiple medications: attempt to identify MOST likely offending agent and discontinue it AND all unnecessary medications.
- Use alternative, pharmacologically distinct agents
- If no alternative may elect to continue offending agent BUT watch for SCAR's (EM/SJS,TEN, serum sickness, exfoliative erythroderma)

Most Common Drug Reaction

- MORBILLIFORM or measles-like pattern
- Most adverse cutaneous reactions to medications represent a benign side effect
- Rare cases, drug eruptions may have associated systemic complications with significant morbidity & mortality

Morbilliform Eruption

- Most frequent of all cutaneous drug reactions
- Maculopapular eruptions often indistinguishable from viral exanthems
- Onset 7-10 days after starting a medication.
- If medication given previously and patient unaware of a developed sensitivity reaction during that previous administration than a reaction may occur in 1-2 days.
- Reactions may occur to unmetabolized amounts of a discontinued medication as long a trace amounts remain (up to 21 days).

- Rash is symmetrical and widespread (torso >extremities> head & palms/soles)
- Itching common
- Rash fades in 1-2 weeks
- Best to discontinue suspected medication
- May fade even if drug continued
- May ‘lead’ to a SCAR if suspected agent continued or reintroduced.

Drug Reaction:Widespread macules & papules (morbilliform)

Drug Eruption: erythematous macules & papules (morbilliform)

Drug Widespread erythematous macules & papules (confluence)

Drug reaction: morbilliform erythematous eruption

Widespread erythematous papulopustular eruption

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Closeup papulopustular eruption

Maculopapular confluent eruption

Erythematous macules & patches, papules and subtle plaques

Erythematous macules & subtle papules : confluence/ early plaque

Widespread morbilliform eruption

Widespread morbilliform eruption

Purpuric Drug Eruption

URTICARIA:HIVES

- Pruritic, transient, edematous, red plaques
- Evanescent: last less then 24 hr
- Acute (<6wks) / chronic (>6wks)
- Mainstay of therapy is antihistamines:
  sedating vs non-sedating
- Better to find the cause / trigger and eliminate / discontinue such

Urticaria

Urticaria

7 I's & 2 P's of Urticaria

- Infections
- Infestations
- Inhalants
- Ingestants
- Injectants
- tIssue products
- Idiopathic
- Physical
- Psychological

Rx mainstay: ANTIHISTAMINES

- First-generation: induce high levels of impairment & sedation
  - diphenhydramine
  - chlorpheniramine
  - brompheniramine
- Second-generation: “non-sedating”
  - loratadine
  - desloratadine
  - cetirizine
  - fexofenadine
  - levocetirizine

If no resolution as expected

- ? Another drug
- ? Another diagnosis
- ? drug cross-reaction
- Skin Bx: hypersentivity vs. SJS/TEN/EM
- Watch for symptom changes (skin tenderness, bullous or target lesions, mucosal involvement) (liver- LFT's / renal-RFT's/ hematological abnormalities – change wbc, increase eosinophils, decrease in platlets / myositis – creatine kinase)

Severe Cutaneous Adverse Reactions : SCAR

- Stevens-Johnson Syndrome: SJS
- Toxic Epidermal Necrolysis: TEN
- Drug Reaction with Eosinophlia & Systemic Symptoms: DRESS
- Acute Generalized Exanthematous Pustulosis: AGEP
- Erytheroderma / Exfoliative Erytheroderma
- Drug Induced Vasculitis

SCAR warning signs

- FEVER
- Hypotension
- Myalgias or weakness
- Respiratory distress
- Facial swelling
- Scleral icterus, jaundice
- Bullae formation or target lesions
- Skin pain or tenderness
- Mucosal inflammation (ocular, oral, genital)
- Lymphadenopathy

Common Offenders

- Non-steroidal anti-inflammatory drugs
- Sulfa-based medications
- Antibiotics
- Anticonvulsants

Rx:

- Supportive therapy : antihistamines (hydroxyzine 25-50 mg tid to qid)
- Topical therapy: plain emollients or medium potency topical corticosteroids (triamcinolone 0.1% ointment bid)
- Patient & first degree relatives aware of drug/drug class
- Medical alert cards or jewelry tags (medical alert bracelet)

Alternate Rx : Systemic Steroids

- Prednisone 0.5 – 2 mg / kg / day
- 4-5 days at ‘high dose’ then taper (total 10-14 days).

Erythema Multiforme

- Acute inflammatory disease characterized by target-shaped lesions
- Most often associated with herpes simplex Mycoplasma pneumoniae, and URI's
- Also assoc. with connective tissue dis, drugs, internal malignancy, x-ray therapy
- Multiform lesions: macules, papules, urticarial-like, vesicles & bullae
- Classic iris or target lesions

Erythema Multiforme: many forms of redness

Erythema Multiforme: early target lesions

Erythema Multiforme: macules, papules

Erythema Multiforme: urticarial-like/early target like lesions

Erythema Multiforme: classical iris lesion

Erythema Multiforme: dusky iris lesiond (note 2 vesicles)

Eythema Multiforme: often palm & sole involvement

Erythema Multiforme: hands/palms

Erythema Multiforme: dorsum of hands (note vesicles)

Erythema Multiforme: blotchy macules & early targets of palm

Erythema Multiforme: classical iris/target lesions of palms

Erythema Multiforme: secondary to URI (strep. Infection)

Erythema Multiforme: secondary to vaccination

Stevens-Johnson Syndrome

- Sever blistering mucocutanous syndrome of at least two mucous membranes
- Associated with drugs (phenytoin, phenobarbital, carbamazepine, sulfonamides, and aminopenicillins. Also Mycoplasma pneumoniae

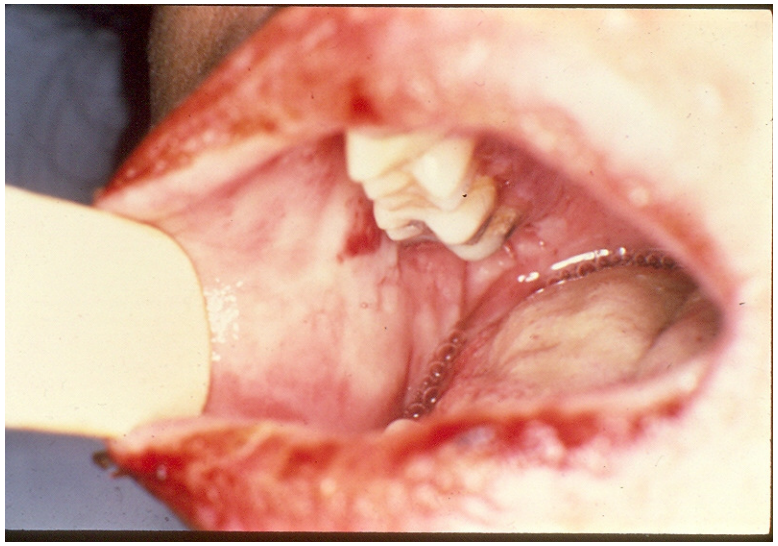
Stevens-Johnson Syndrome: generalized EM-like rash

Stevens-Johnson Syndrome: palm& sole as in EM

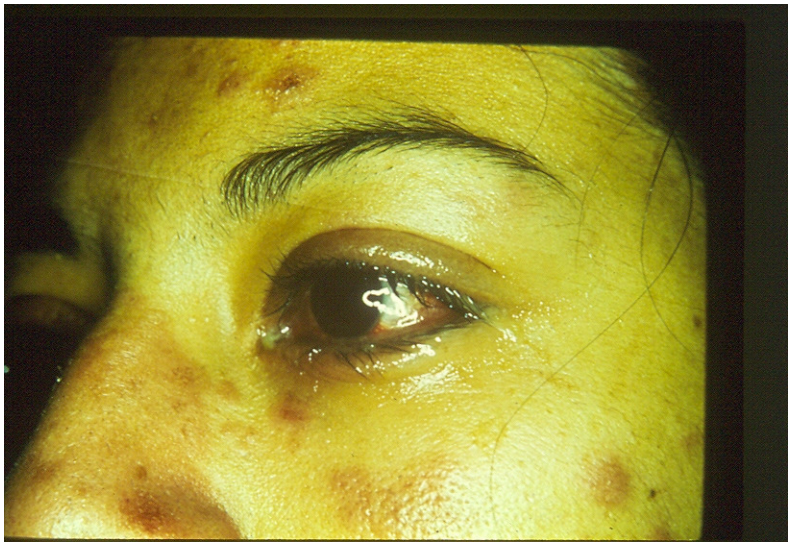
Stevens-Johnson Syndrome mucous membrane involvement

Stevens-Johnson Syndrome: mouth& lips

Stevens-Johnson Syndrome: oral mucosa



Stevens-Johnson Syndrome: ocular mucosa/conjunctiva



Stevens-Johnson Syndrome; genital mucosa

Stevens-Johnson Syndrome: EM & 2+ mucosal surfaces

SJS = EM major

- EM minor- esp. assoc with HSV
- typical target lesions
- self limited
- EM major- typical & atypical target lesions
- severe mm changes at 2+ sites
- often an adverse drug reaction
- associated with many different
- infections

Rx SJS

- Often hospitalized
- Rx guided by ‘cause’
- D/C suspected medication
- Rx suspected infection
- Supportive care, symptomatic care, wound care
- Use of systemic steroids ???
- use ? associated with complications

Toxic Epidermal Necrolysis (TEN)

- Drug induced TEN- injury at dermal epidermal junction- ‘full thickness wound”
- Staphylococcal Scalded Skin Syndrome- injury high in the epidermis due to an endotoxin

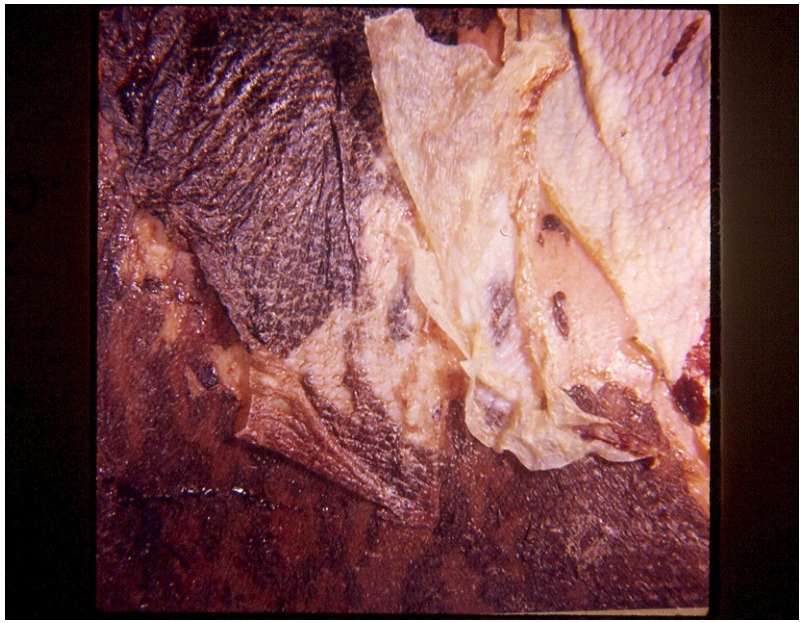
Drug induced TEN

- Sulfonamides, antimalarials, anticonvulsants, NSAID, & allopurinol
- HIV &SLE pts at higher risk
- Can be ppt. by recent immunization, viral infection (cytomegalovirus, E-B virus, HSV, Varicella-Zoster virus & hepA), mycoplasma, strep inf, syphilis, histo, coccidio & tuberculosis

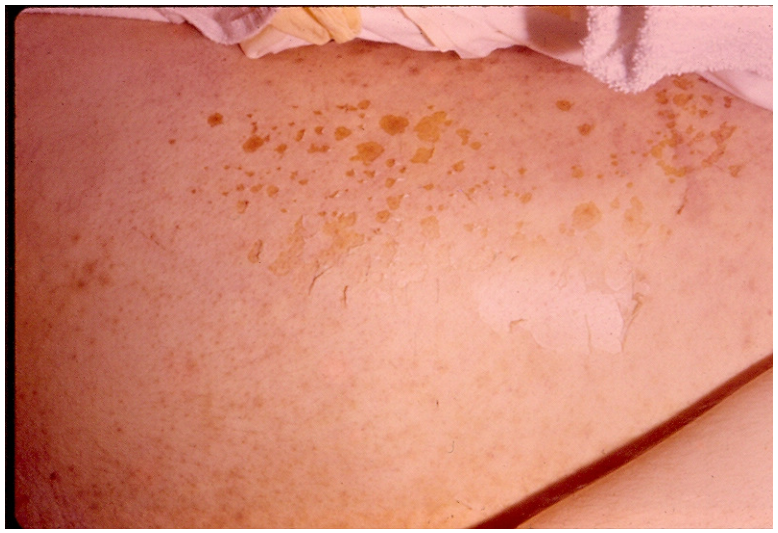
TEN

- Diffusely red (sunburn-like) TENDER skin with scattered target and bullae that quickly coalesce and result in widespread “full thickness” skin sloughing

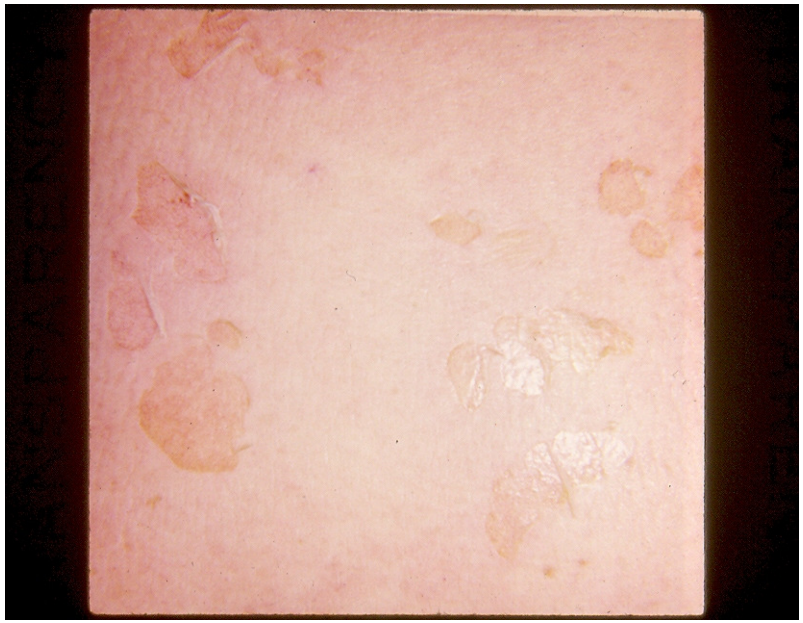
Toxic Epidermal Necrolysis: sheets of full thickness epidermis



Toxic Epidermal Necrolysis
TENDER / skin sloughs/peels away



Nikolsky's sign: with pressure the skin separates easily



TEN: equivalent to a full thickness second degree burn

Toxic Epidermal Necrolysis: sheets of skin slough off

TEN: treated in a burn unit

Exfoliative Erythroderma

- 50% Pre-existing Dermatoses: Atopic Dermatitis, Psoriasis, Seborrheic Dermatitis
- 15% Drug Reaction
- 10%Cutaneous T cell Lymphoma,Leukemia (CLL)
- 25%Idiopathic

Exfoliative Erythroderma: look at elbows

Exfoliative Erythroderma

Exfoliative Erythroderma:

Erythroderma/ Exfoliative Erythroderma

- Heat loss: chills (shiver) not a true rigor (unless septic)
- Fluid & calorie loss, weight loss
- Sepsis due to loss of skin barrier

Rx

- High protein diet, B vitamin and Fe supplements, fluid & electrolytes
- Hydroxyzine (for itch and sedation)
- Systemic steroids 1-3 mg/kg/day
- Do not use steroids in psoriasis patients- use cyclosporin

Acute Generalized Exanthematous Pustulosis (AGEP)

- Acute erythematous edematous skin
- NON-follicular small sterile pustules
- Begins folds & face, within hours diffuse
- Mild non-erosive oral mucous membrane changes
- Fever/elevation wbc, polys & eos/ lymphadenopathy/acute renal failure/ mild elev of LFTs

Etiology of AGEP

- Antibiotics- beta-lactams / aminopenicillins & macrolides
- Antifungals
- NSAID
- Piroxicam
- Quinolones
- Also: CMV
- Parvovirus B19
- Chlamydia
- Mycoplasma pneumoniae

Drug Reaction with Eosinophilia & Systemic Symptoms (DRESS)

- DRESS Syndrome = drug-induced hypersensitivity syndrome = dilantin / phenytoin hypersensitivity syndrome
- Morbilliform cutaneous eruption
- Associated fever
- lymphadenopathy
- hematological abnormalities
- multi-organ manifestations
- 10% mortality usually from fulminant hepatitis & hepatic necrosis

DRESS Syndrome

- Erythematous morbilliform rash of face, upper trunk, upper & lower extremities
- May have vesicles, bullae, atypical targetoid plaques and purpura.
- Also may have sterile follicular & non-follicular small pustules
- May evolve to an exfoliative dermatits / exfoliative erytheroderma
- Mucous membrane erosions
- Facial edema-96%pt (mistaken for angioedema)

Multi- System Disease

- Lymphatic- 75% tender cervical, axillary, inguinal lymphadenopathy
- Hematologic- lymphopenia precede a marked leukocytosis / 30% eosinophilia (may be delayed 1-2 weeks) / thrombocytopenia
- HEPATIC: 70-95% abnormal LFT's (ALT) 10% mortality usually from fulminant hepatitis & hepatic necrosis

- Renal 11% hematuria, proteinuria, interstitial nephritis
- Pulmonary- abnormal PFTs, pneumonitis
- Cardiac- myocarditis
- Neurologic- mengitis, encephalitis
- Gastrointestinal- gastroenteritis
- Endochrine – thyroiditis, pancreatitis
- Note- myocarditis & thyroiditis may occur up to 2 yrs after ‘recovery’ from DRESS

Drugs causing DRESS

- Anticonvulsants esp. phenytoin
- Sulfonamides including dapsone

- Often a later onset (2-6 weeks) & a longer duration than other drug reactions

- DRESS may involve reactivation of herpes virus, esp HHV-6 but also HHV-7, EBV, CMV
- Culprit drugs may not only affect epigenetic control mechanism, thereby promoting viral reactivation but also induce an antiviral T-cell response by interaction with the major histocompatibility complex receptor in individuals with genetic suscepitibility factors

DRESS Rx

DISCONTINUE OFFENDING AGENT

Steroids

- IVIG
- Plasmapharesis
- Immunosuppressive drugs
- cyclophosphamide
- cyclosporine
- interferons
- muromonab-CD3
- mycophenolate mofetil
- rituximab

SCAR patients

- Patient & first degree relatives aware of drug/drug class
- Medical alert cards or jewelry tags (medical alert bracelets)