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 epidemiology
- 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 asymptomatic
- 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 & buttocks 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 DOES 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 meningococccemia
Epstein-Barr virus

- Fever
- Sore throat / pharyngitis
- Lymphadenopathy
- Periorbital edema
- Abdominal pain
- Myalgias
- Hepatosplenomegaly
- Occasionally vesicular, urticarial or petechial rash
• Laboratory work as indicated by Hx & P.Ex
• Skin Biopsy: non-specific but may help to differentiate from SSSS & drug hypersensitivity reactions
Drug Eruptions

• Sudden onset
• Symmetrical
• Widespread: especially 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, ocular)
- 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
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: hypersensitivity 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 Eosinophilia & Systemic Symptoms: DRESS
- Acute Generalized Exanthematous Pustulosis: AGEP
- Erythoderma / Exfoliative Erythoderma
- 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 lesion (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 mucocutaneous 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 Exantherematous 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 dermatitis / exfoliative erythrodema
- 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- meningitis, encephalitis
• Gastrointestinal- gastroenteritis
• Endocrine – 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 susceptibility 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)