1) Erythema - Dr. Kazhan

Flushing

- It is transient diffuse redness (erythema) of face & neck
- Causes:
  - *Drugs*: Niacin, cyclosporine, chemotx, vancomycin, contrast dye, tamoxifen, high dose prednisolone
  - *Others*: red pepper, alcohol, food poisoning, Carcinoid, Mastocytosis, Pheochromocytoma, Menopause, oophorectomy.

Erythema (Redness)

- Is blanchable redness (hyperemia) of the skin. A number of reactive skin conditions are referred to as erythemas. These Includes:
  - A number of toxic erythema related to bacterial and viral infections.
  - Erythema multiforme (EM).
  - Erythema nodosum, and gyrate (figurate).

Erythema Palmare

- Causes:
  - Elevated Estrogen
  - Cirrhosis
  - Liver CA metastatic
  - Pregnancy

Erythema Multiform

Classification

- Erythema multiforme minor is not very serious. Most erythema multiforme is caused by herpes simplex or mycoplasma infections.
- Erythema multiforme major is more severe. It is also known as Stevens-Johnson syndrome. This form is usually caused by reactions to medicines, rather than infections.

Clinical Features

- Self-limited, recurrent, young adults, spring/fall
- Mild constitutional symptoms or no prodrome 1-4 weeks
- Lesions evolve over 24-48 hours
- “Target” or “iris” lesions are diagnostic
  - Central dusky purpuric area
  - Elevated edematous pale ring
  - Surrounding macular erythema

Usually associated with orolabial HSV

Antivirals improve it and steroids worsen it

Appears 1-3 weeks after the herpes lesion

Sometimes EMM comes without herpes.

Again we know that more often herpes comes without EMM.
Oral Erythema Multiforme

- Oral only in 45%, lip & oral 30%
- Tongue, gingiva and buccal mucosa are the most severely affected.
- Erosions +/- a pseudomembrane
- It is important to r/o Candida, because topical antifungal therapy leads to improvement in 40% of cases in which Candida is found, otherwise prednisone.

EM Treatment

- Depends on etiology.
  - If HSV: Treat HSV, sunblock.
  - If SJS or TEN, stop medications such as sulfonamides, antibiotics, NSAIDS, allopurinol, anticonvulsants.
  - Look for history of mycoplasma or radiation therapy.
  - SJS, TEN: treatment in Burn unit, IVIG, Steroids etc.

Erythema Nodosum

- Young adult women
- Crops of bilateral deep tender nodules, pretibial
- Overlying skin shiny, red.
- Onset acute with arthralgia, malaise, edema
- 2-3 days lesions flatten and have a bruised appearance, may last days or weeks
- Reactive Process
- Histopathology: Septal panniculitis

Erythema Toxicum Neonatorum

- Occurs in most healthy full term newborns, usually on 2nd -3rd day.
- Multiple papules that rapidly evolve into pustules with an erythematous base
- Lesions may become confluent, especially on the face
- No fever, gone by 10th day
- Ddx: Miliaria, Herpes, Bacterial folliculitis, scabies
- Pustule smear revealing eosinophils is diagnostic.
- Bx: shows folliculitis of eos and neuts

Stevin Johnson syndrome/ Toxic Epidermal Necrolysis

SJS/TEN:

- Lesions: Small blisters on dusky purpuric macules or atypical targets
- Mucosal involvement common
- Prodrome of fever and malaise common
- Stevens-Johnson Syndrome:
  - Rare areas of confluence.
  - Detachment <= 10% Body Surface Area
Toxic Epidermal Necrolysis:

- Confluent erythema is common.
- Outer layer of epidermis separates easily from basal layer with lateral pressure.
- Large sheet of necrotic epidermis often present.
- >30% BSA involved.

Presentation

- *Fever* (often >39) and *flu-like illness* 1-3 days before mucocutaneous lesions appear
- Confluent *erythema*
- Facial edema or central facial involvement
- Lesions are *painful*
- Palpable purpura
- Skin necrosis, blisters and/or epidermal detachment
- Mucous membrane erosions/crusting, sore throat
- Visual Impairment (secondary to ocular involvement)
- Rash 1-3 weeks after exposure, or days after 2nd exposure

Epidemiology

- 2-7/million people/year
- SJS: age 25-47, TEN: age 46-63
- Women: >60%
- Poor prognosis:
  - Intestinal/Pulmonary involvement
  - Greater extent of detachment
  - Older age
- Mortality:
  - SJS: 5%
  - TEN: 30%

Risk Factors

- HIV infection
- Genetic factors
  - Certain HLA types
  - “Concomitant viral infections
- Underlying immunologic diseases
- Physical factors
  - UV light, radiation therapy
- Malignancy
- Higher doses of known offenders

Pathogenesis

- Secondary to cytotoxicity and delayed hypersensitivity reaction to the offending agent.
- Antigen is either the implicated drug or a metabolite.
- Histopathology:
  - Subepidermal split with cell-poor bullous.
  - Epidermis shows full thickness necrosis.

Etiologies

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<th>Infections</th>
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<td>Sulfonamide antibiotics</td>
<td>(e.g. Mycoplasma pneumonia)</td>
<td>Vaccinations, Systemic diseases, Chemical exposure, Herbal medicines, Foods</td>
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Differential Diagnosis for Vesicular or Bullous Rash

- Dermatitis Herpetiformis (Associated with gluten intolerance)
- Cicatricial Pemphigoid (Mucosal involvement, sometimes cutaneous)
- Bullous Pemphigoid (Often affects the elderly)
- Pemphigus (Affects middle-aged or elderly)
- Varicella/Zoster Virus
- Herpes Simplex Virus
- Hand-Foot-Mouth Disease (Enteroviruses)
- Linear IgA Disease (Itchy, ring-shaped, no internal disease)
- Contact Dermatitis
- Erythema Multiforme
- Staphylococcal Scalded Skin Syndrome
- Bullous Impetigo
- Toxic Shock Syndrome
- Paraneoplastic Pemphigus
- Cutaneous emboli
- Diabetic Bullae
- Porphyria Cutanea Tarda
- Porphyria Variegata
- Pseudoporphyria
- Bullous dermatosis of Hemodialysis
- Coma Bulloae
- Epidermolysis Bullosa Acquisita

Treatment

- Early diagnosis - biopsy
- Immediate discontinuation of offending agent
- Supportive care – pay close attention to ocular complications
- IV hydration
- Antihistamines
- Analgesics
- Local v. systemic corticosteroids
- Possible treatment in burn unit, wound care
- IVIg?

Urticaria

- The term urticaria is widely used to describe an eruption of weals. It is now also increasingly being used to define a disease characterized by short-lived itchy weals, angio-oedema or both together.
- Urticaria is a superficial swelling of the skin (epidermis and mucous membranes) that results in a red, raised, itchy rash. It is also known as hives, nettle rash, or weals.

Pathogenesis

- Increased capillary permeability, which allows proteins and fluids to extravasate.
- Due to histamine release from mast cells degranulating, which in turn recruits eosinophils, neutrophils and basophils.
- Other triggers are leukotrienes (slow reacting substances of anaphylaxis), prostaglandins, proteases, bradykinins…etc.

History: Use a questionnaire!

- Recent illness (eg, fever, sore throat, cough, rhinorrhea, vomiting, diarrhea, headache) INFECTIOUS: STREP, HEP C, H. PYLORI
- Medication use (especially C1 esterase inhibitors, which result in angioedema, as well as anesthetics, penicillins, cephalosporins, sulfas, diuretics, aspirin, nonsteroidal anti-inflammatory drugs [NSAIDs], iodides, bromides, quinidine, chloroquine, vancomycin, isoniazid, antiepileptic agents)
- Travel (rule out amebiasis, malaria, helminthics)
- New foods (eg, shellfish, fish, eggs, cheese, chocolate, nuts, berries, tomatoes, alcohol)
- Perfumes, detergents, lotions, creams, or clothes
- Exposure to new pets (dander), dust, mold, chemicals, or plants
- Pregnancy (PUPPP)
- Contact with nickel (eg, jewelry, jean stud buttons), rubber (eg, gloves, elastic bands), latex, industrial chemicals, and nail polish
- Sun exposure or cold exposure, exercise
Chronic Urticaria

- 1/3 of these patients have circulating functional histamine-releasing autoantibodies that bind to the high-affinity IgE receptor producing mast cell-specific histamine releasing activity
- Get a good drug history: NSAIDS, Antibiotics

Histopathology: collagen bundles separated by edema, perivascular infiltrate

Urticaria & Angioedema DDx:

- Clinical diagnosis:
  - DDx: Urticarial Vasculitis, Bullous Pemphigoid, pemphigoid gestationis, DH, Sarcoidosis, CTCL (Cutaneous T cell leukemia)
  - Most of the diseases listed above have lesions that last longer than 24 hours.
- Biopsy: for urticarial lesions that last > 24 hours.

Urticaria Evaluation

- Good History & Physical examination is most cost effective
- Dental and sinus x-rays can be of benefit
- Order laboratory tests based only on symptoms and signs from H&P including:
  - Thyroid, LFTs, Hepatitis panel, ANA, CBC.
  - Eosinophilia -> search for parasites
  - Food skin tests.

Treatment

- Oral AntiHistamines, multiple if necessary
- It has been found that in “refractory” urticarias, 58% of patients preferred H1+H2 combinations.
- Oral steroids rarely helpful
- Foods to avoid: Fish and shellfish
- Pork
- Garlic, onions
- Mushrooms
- Tomatoes, melons, strawberries, citrus fruits, pickles and relishes
- Nuts, peanuts, cheese
- Remove suspected food x 3 weeks then resume

Anaphylaxis

- Acute, life threatening urticaria/angioedema 90%, SOB 60%
- Onset: peak severity within 5-30 minutes
- Most common causes of serious anaphylactic reactions are: Anitbiotics, especially Penicillines, NSAIDS, Radiographic contrast dyes
- 2nd Most Common cause – hymenoptera (type of sea food), shellfish
- Mortality rate less than 10%, Still account for vast majority of fatal reactions, peak onset 5-30 minutes.
- One of every 2700 hospital patients. 500 annual fatalities
- Treatment: 0.3 - 0.5mL dose of 1:1000 dilution of epinephrine 10-20 minutes
- IV corticosteroids, aminophyliline, O2, glucagon, intubation, IV fluids.
Angioedema

It is similar to urticaria (hives), but the swelling occurs beneath the skin instead of on the surface. Angioedema is characterized by deep swelling around the eyes and lips and sometimes of the genitals, hands, and feet. It generally lasts longer than hives, but the swelling usually goes away in less than 24 hours.

Hereditary Angioedema

- 2nd to 4th decade, + Family history, AD
- May occur each 2 weeks, lasting 2 to 5 days
- Eyelid and lip involvement.
- Face, hands, arms, legs, genitals buttocks, stomach, intestines, bladder affected.
- N&V, Colic, may mimic Appendicitis
- Triggers: minor trauma, surgery, sudden changes in temperature or sudden emotional stress
- Presence of urticaria rules out HA
- NO PRURITIS OR URTICARIA, + PAIN
- Autosomal Dominant
- Low C4, C1, C1q, C2 levels
- Low or dysfunctional plasma C1 esterase inhibitor protein.
- Tx of choice: fresh frozen plasma, stanazol, tranexamic acid
- 25% of deaths due to HA are the result of laryngeal edema
- Treatment:
  - For acute HA is fresh frozen plasma
  - Stanazol useful for short-term prophylaxis in patients undergoing dental surgery, endoscopic surgery or intubation.
  - Tranexamic acid in low doses has few side effects and useful for acute or chronic HA.

Acquired Angioedema

- Symptoms same as HA, but NO family hx.
- Acute evanescent circumscribed edema
- Affects most distensible tissues: eyelids, lips, earlobes, genitalia, mouth, tongue, larynx.
- Swelling is subcutaneous, not dermal.
- Overlying skin is not affected.

Physical Urticarias

- 20% of all urticarias
- Types:
  - Dermatographism
  - Cholinergic/Adrenergic
  - Cold/Heat
  - Solar
  - Pressure
  - Exercise induced
  - Aquagenic
  - Vibratory Angioedema
**Dermatographism**
- Sharply localized wheal and flare seconds to minutes after stroking skin
- 2% to 5% of the population
- Associated with penicillin induced urticaria, Pepcid (famotidine), hypothyroidism, hyperthyroidism, infectious disease, diabetes mellitus, onset of menopause
- Treatment: Oral AntiHistamines.

**Cholinergic Urticaria**
- Acetylcholine induced
- Tiny punctate extremely pruritic wheals or papules 1-3mm in diameter surrounded by erythema
- Most commonly sites affected trunk and face, spares palms & soles
- *Triggers:* exercise, heat,
- *Tx:* Cold shower, OAH high dose
- *Provoke:* Methacholine skin test, heat

**Adrenergic Urticaria**
- Norepinephrine induced
- Small 1-5mm papules, +/- pale halo
- 10-15 minutes after emotional upset, coffee or chocolate
- Serum adrenaline elevated, histamine normal.
- *Tx:* Propranolol 10mg QID
- *Provoke:* 3 to 10 nanograms noradrenalin intradermally

**Cold Urticaria and Angioedema**
- MC sites: Face/hands, occurs with rewarming
- 25% Patients atopic
- *Tx:* (Cyproheptadine) PERIACTIN 4mg TID
- *Trigger:* repeated colder exposures.
- *Test:* Ice cube in saran wrap x 5-20 min.
- *Assoc:* Cryoglobulins, Myeloma, Syphilis, Hepatitis, Mononucleosis
- Familial variant
  - *Tx:* Stanazol

**Heat Urticaria**
- Provoked in 5 minutes
- Heat > 109.4 farenheit (43 C)
- Features:
  - Burns, stings, red, swollen, indurated
  - May become generalized with cramps, weakness, flushing, salivation and collapse
- *Tx:* heat desensitization
  - Provoke heated cylinder 122 F x 30 min.
Solar Urticaria

- Classified by the wavelength of light causing it.
- Visible light may cause it so sunscreens may be of little help.
- Treatment:
  - Sun Avoidance.
  - OAH
  - PUVA, Repetetive phototherapy.

Pressure Urticaria

- 3 to 12 hours after local pressure has been applied.
- MC sites: feet/walking and buttocks/sitting
- Arthralgias, fever, chills, leukocytosis can occur
- Tx: ORAL STEROIDS HELPFUL, ANTIHISTAMINES NO HELP!
- Provoke: 15 lb. weight x 20 minutes

Exercise Induced Urticaria

- Not related to body temperature
- Wheals are larger than those seen in cholinergic urticaria
- Starts after 5-30 minutes of exercise
- Patients often atopic
- Avoid celery and gliadin or other food allergy
- Tx: OAH

Vibratory Angioedema

- Autosomal Dominant or acquired
- Usually occupational in origin
- Plasma histamine levels elevated during attacks
- Provocation test: Laboratory vortex vibration applied for 5 minutes
- Tx: OAH

Aquagenic Urticaria

- Water, seawater, tears, sweat, saliva at any temperature may provoke
- Immediately or within minutes and clear within 30-60 seconds.
- Wheezing, dysphagia, SOB may accompany
- Water soluble antigens the etiology?
- Tx: Petrolatum, OAH, PUVA.

Purpura

Multifocal extravasation of blood into the skin.

Types:

- Petechiae <3mm
- Ecchymosis >3 mm
- Vobices (vibex) – Linear
- Hematoma – pool-like collection
Causes:

- Coagulation defects (hemophilia)
- Thrombocytopenia (low platelets no)
- Abnormal platelets’ function (von Willebrand’s disease)
- Drugs (Aspirin)
- Infections (meningococcal septicemia)
- Vasculities & Vascular defects
- Idiopathic

Investigations:

- Complete blood count
- PT and PTT

Treatment: according to the cause

Mastocytosis

It is a disorder characterized by mast cell proliferation and accumulation within various organs, most commonly the skin.

Manifestations:

- Cutaneous
- Systemic

80%: cutaneous - children

Several clinico-pathological categories

No sex predilection

Good prognosis, spontaneous regression

Adults: over 30 years, mostly: assoc. Systemic Mastocytosis.

20%: systemic – adults