Urticaria

- Wheals - superficial dermal swellings
  - Pink and pruritic
- Angioedema – deeper dermal/subcutaneous swellings
  - Pale and painful

Acute vs. Chronic Urticaria

- **Acute Urticaria**
  - Evolves over days-weeks, wheals lasting < 12 hrs, & complete resolution in 6 wks

- **Chronic Urticaria**
  - Daily urticaria and/or angioedema episodes lasting > 6 wks
  - Adults predominantly; 2:1 F:M
  - 1/3 of pts have circulating histamine-releasing autoantibodies that bind to the high-affinity IgE receptor→ mast cell-specific histamine releasing activity
**Acute Urticaria Etiologies**

- Acute Urticaria
  - Infections - strep common, Hep B and C
  - Drugs - think Penicillins or related agents (dairy)
  - Foods - chocolate, shellfish, nuts, peanuts, tomatoes, strawberries, melons, pork, dairy
  - Food additives - both natural and synthetic
  - Stress, menthol, neoplasms (Hodgkin & CLL), inhalants, alcohol, genetics

**Chronic Urticarial Etiologies**

- Chronic Urticaria
  - More than 25% are idiopathic
  - Physical Urticarias - cold, heat, dermatographic, cholinergic, aquagenic, solar, vibratory, exercise induced
  - Hormone imbalance

**Urticaria Diagnosis**

- Largely clinical and based on detailed history and PE
- If wheals last > 24 hours, biopsy
- Angioedema w/o urticaria, check C4 level; if low evaluate C1 esterase inhibitor
- Review med list
Urticaria Dx

- Dental and sinus x-rays can be of benefit- esp. if palpable tenderness over ethmoid or maxillary sinuses
- Order laboratory tests based only on symptoms and signs from H&P including: TSH, LFTs, Hepatitis panel, ANA, CBC
- Eosinophilia: search for parasites
- Food skin tests
- Challenges for physical urticarias

Pathogenesis

- Histamine released mast cell degranulation → capillary permeability → extravasation of proteins and fluids
- Histamine recruits eosinophils, neutrophils & basophils
- Other agents causing capillary permeability: serotonin, leukotrienes, prostaglandins, proteases, bradykinins

Urticaria DDx:

- DDx for fixed lesions lasting more than 24 hours
  - Urticarial Vasculitis
  - Bullous Pemphigoid
  - Granuloma Annulare
  - EM
  - Sarcoidosis
  - CTCL
- Most of the diseases listed above have lesions that last longer than 24 hours
- Biopsy urticarial lesions that last > 24 hours
Acute Urticaria Treatment

- **Tx:** *Antihistamines are the mainstay*
- Avoid triggers
- Refractory acute urticaria- 3 week taper of systemic corticosteroids (less rebound)
- Severe reactions –respiratory and CV support and 0.3mL dose of epinephrine 1:1000 Q10-20 min.
- Half strength dilution in children

Chronic Urticaria Treatment

- Mainstay is **DAILY antihistamines**, not prn;
  - Second generation preferred (cetirizine, levocetirizine, fexofenadine, loratadine) for their lipophilic, non-sedating effects
  - Doxepin (TCA w/ H1 activity) added to antihistamine
  - Combo H1+H2 (hydroxyzine and cimetidine/ranitidine)
  - Do not use cimetidine/ranitidine alone-interfere w/ feedback inhibition of histamine
- Cool bathing
- Pramoxine, Sarna
- Multiple second line therapies: phototherapy, CCBs, antimalarials, gold, azathioprine,
  - No real role for topicals
  - Systemic steroids are impractical

Chronic Urticaria Treatment Cont…

- Omalizumab
  - Anti IgE
  - FDA approved 2014
  - 150 mg and 300 mg doses
  - Monthly injections
  - Monitoring for anaphylaxis
Anaphylaxis

- Acute and life threatening immunologic reaction
- Scalp pruritus, diffuse erythema, urticaria, or angioedema
- (+/-) Brochospasm, laryngeal edema, hypotension, cardiac arrhythmia
- Onset: peak severity within 5-30 minutes
- MC causes of serious anaphylactic reactions are: antibiotics, especially PCNs, and radiographic contrast dyes
- 2nd MC cause – hymenoptera stings, followed by ingestion of crustaceans/other food allergens

Anaphylaxis

- 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
- Tx: 0.3 - 0.5mL dose of 1:1000 dilution of epinephrine SQ q 10-20 minutes
- IV methylprednisolone 50mg q6h x 2-4 doses
- diphenhydramine, aminophylline, nebulizers, metaproterenol, O2, glucagon, intubation
Angioedema

- Acute, circumscribed edema affecting eyelids, lips, earlobes, genitalia, and mucous membranes
- Subcutaneous or deep tissue swelling, only slightly tender
- Overlying skin is unaltered, edematous, or rarely ecchymotic
- 2 subsets
  1. “deep urticaria” = angioedema +/- urticaria; pruritus present
  2. Angioedema w/ C1 esterase inhibitor deficiency; pain present
- Related to ACE-Is

Hereditary Angioedema (HA)

- AD, + family history, presents 2nd to 4th decade
- Episodes may occur q2 weeks, lasting 2 to 5 days
- Face, hands, arms, legs, genitals, buttocks, stomach, abdominal organs, upper airway
- Little response to antihistamines, epinephrine, or steroids
- Triggers: minor trauma, surgery, sudden changes in temperature or sudden emotional stress
- NO urticaria or itching

Hereditary Angioedema

- AKA Quincke’s Edema - three phenotypic types
- Low C4, C1, C1q, C2 levels in Types I & II
- Low or dysfunctional plasma C1 esterase inhibitor protein
- 25% of deaths are from laryngeal edema
Phenotypic forms of HA

- **Type I** – LOW serum levels of **NORMAl** C1 esterase inhibitor protein (C1-EI)
- **Type II** – NORMAL or elevated levels of **DYSFUNCTIONAL** C1 esterase inhibitor protein
- **Type III** – Normal C1-EI function, normal complement, normal C4 concentrations
- **C4 is best screening test**, it will be low in types I and II, as will C1, C1q, and C2 levels

HA - Treatment

- TOC for HA types I&II is **fresh frozen plasma** or replacement therapy with concentrates
- Stanazol useful as short-term prophylaxis for dental surgery, endoscopic surgery, or intubation
- Tranexamic acid in low doses has few side effects -- useful for acute or chronic HA
- Type III will NOT respond to C1-EI replacement but does respond to danazol

Acquired C1 Esterase Inhibitor Deficiency

- Symptoms same as HA, but **NO family Hx** and acquired after 4th decade
- Also **NO** associated pruritus or urticaria
- Subdivided into acquired angioedema-I, II, and idiopathic
  - Acquired angioedema-I: rare & associated with lymphoproliferative diseases;
  - Acquired angioedema-II: extremely rare w/definite autoantibodies to C1-EI
- Tx:
  - Angioedema-I = Replacement of E1-C1 w/ fresh frozen plasma, plasma-derived C1 inhibitor, or recombinant human C1 inhibitor; danazol
  - Angioedema-II = Immunosuppressives, plasmapheresis, systemic corticosteroids (temporarily); **NO** androgens
Episodic Angioedema w/ Eosinophilia

- Episodic angioedema may occur w/ fever, weight gain, eosinophilia, or elevated major basic protein
- NOT uncommon, no underlying disease
- Increased IL-5 levels
- Tx = systemic steroids, antihistamines, IVIG

Atopic Dermatitis

- Complex inflammatory skin disorder
  - Intense pruritus is hallmark
    - "itching precedes the rashes"
  - Cutaneous hyperreactivity
  - Immune dysregulation – atopic diathesis
  - Chronic condition with exacerbation episode and remission
  - Affects all ages; but more common in kids

Atopic Dermatitis

- Epidemiology
  - Prevalence is increasing in western and developed countries (3x fold)
  - Remains low in agricultural countries
  - Lifetime Prevalence in US
    - Children: 10-20%
    - Adults: 1-3%
Atopic dermatitis is a syndrome

Infantile
2 months to 2 years

Childhood
2 years – 10 years
Infantile Atopic Dermatitis
- Is about 60% of AD, present in the first year of life, after 2 months of age
- Begin as itchy erythema, scaling of cheeks
- May desquamate leading to erythroderma
- Buttocks and diaper area frequently spared
Atopic Dermatitis

- Partial or even complete remission in summer and relapse in winter
- Worsening was observed after immunizations and viral infection
- May exacerbation with egg, peanut, milk, wheat, fish, soy, and chicken
- Most AD patients do NOT have food allergy

Ichthyosis Vulgaris

- Present in up to 50% of AD
- Autosomal Dominant
- Defect in profilagrin synthesis
- Present with fine, whitish adherent scale, worse on extensor extremities, spares flexures
**Vascular Stigmata**

- Headlight Sign
  - Perinasal pallor
  - Periorbital pallor

White dermographism – blanching of the skin at the site of stroking with a blunt instrument ➔ cause edema and obscure color of underlying vessels

**Ophthalmologic Stigmata**

- Up to 10% of patients with Atopic dermatitis develop cataracts
- Keratoconus is an uncommon finding, occurring in about 1% of atopic dermatitis patient

**Bacterial Infections**

- Staph Aureus is found in more than 90% of chronic eczematous lesions
- Any flaring of atopic dermatitis must be evaluated for 2nd infection
- Treatment of atopic dermatitis with topical steroid is associated with reduced numbers of pathogenic bacterial on surface
- Antibiotic option is included cephalosporin, bactrim, clindamycin and doxycycline (in older patient)
Eczema Herpeticum

- Atopic patients have increased susceptibility to generalized herpes simplex infection (eczema herpeticum) as well as wide vaccinia infection (eczema vaccinatum) and complicated varicella
- Atopic patients may also develop extensive flat warts or molluscum contagiosum
- Smallpox vaccine is contraindicated in AD patients

Eczema Herpeticum

Eczema herpeticum: typical vesicular lesions on the hand, around the eye, and on the face

Pathogenesis

Diagrams illustrating the pathogenesis of atopic dermatitis, including factors such as stress, irritants, allergens, and immune system components.
Immunology
- In atopic patient, there is T helper cell type 2 dominant
- Activation of Th2 produces IL-4, 5, 10, 13, inhibiting of T-helper 1
  - IL-4, 5 produce elevation of IgE and eosinophilia in tissue and peripheral blood
  - IL-10 inhibits delayed-type hypersensitivity
  - IL-4 downregulates interferon gamma production

Immunology
- Langerhan cells in skin of AD patient also demonstrate abnormalities
  - Directly stimulate helper T-cells without the presence of antigen
  - Selectively activating helper T-cells into a Th2 phenotypes

<table>
<thead>
<tr>
<th>THERAPEUTIC LADDER FOR ATOPIC DERMATITIS</th>
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<tbody>
<tr>
<td>1. Emollients (2)</td>
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<tr>
<td>2. Topical corticosteroids (1)</td>
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<tr>
<td>3. Topical immunomodulators (1)</td>
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<tr>
<td>4. UVB or UVA-UVB (1)</td>
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<td>5. Narrowband (UVB) (2)</td>
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<td>6. Oral PUVA (1)</td>
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<td>7. UVa1 phototherapy (1)</td>
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<td>8. Systemic corticosteroids (2)</td>
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<td>9. Azathioprine (2)</td>
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<td>10. Mycophenolate mofetil (3)</td>
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<td>11. Cyclosporine (short term) (1)</td>
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<td>12. Interferon gamma (1)</td>
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<tr>
<td>13. Intravenous immunoglobulin (1)</td>
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<tr>
<td>14. Other (antihistamines, antibiotics, wet wraps, crude coal tar, leukotriene antagonists, sodium cromoglycate, hydroxycocaine, photopheresis)</td>
</tr>
</tbody>
</table>
1. Repair the Skin
   - Hydration and moisturization
   - Bath or shower followed by emollient or oils (avoid lotions)
     - Gentle cleansers – mild, non-alkali soaps
     - Bathing protocol

Water is not the enemy!

Rehydrate the skin!

Topical Steroids
   - Topical steroid is essential and continue to be first line therapy
     - Anti-inflammatory
     - Decrease Staph Aureus density
     - Agent/duration
       - Severity, distribution, age, vehicle, occlusion
Topical calcineurin inhibitors

- Decrease IL-2 \(\rightarrow\) decrease T helper cells
- Indication
  - Mild, patchy eczema
  - Eyelid involvement
  - Combination with topical steroid
  - Maintenance therapy
- Tacrolimus ointment
  - 0.03% FDA approved for mod-severe AD in older than 2 years old patient
- Pimecrolimus cream
  - 1% cream FDA approved for mild-mod AD in older than 2 years old patient
- Black box labels

2. Control the Itch

- Systemic sedating antihistamine
  - Bedtime dose to break the itch-scratch cycle
  - Hydroxyzine or diphenhydramine
  - Doxepin
    - TCA/anti-H1 and H2
    - Reserved for recalcitrant pruritus
- Systemic nonsedating antihistamine
  - If respiratory allergy is present

3. Treat Infection

- Secondary infection is common
- Treat early and aggressively
- Bleach Baths
- Staph Aureus
  - Cephalosporin or semisynthetic penicillin
  - Culture for MRSA
- Herpes Simplex
  - Systemic antiviral
4. Education and Follow-up

- Lifestyle modification
- Avoid trigger factors
- Risks/benefits
  - Enhance compliance
  - Implement a step-down regimen
  - Treat early flares aggressively

Phototherapy

- Photochemotherapy (PUVA), UVA or broad-or narrow band UVB, may be helpful in severe atopic dermatitis
  - Broad-band UVB is least effective
  - Combination of UVA and UVB is superior

Eczema

- Broad range of conditions that begin as spongiotic dermatitis to lichenified stage
- Three stages:
  - Acute: red edematous plaque which may have grossly visible small grouped vesicles
  - Subacute: Erythematous plaques with scale or crusting
  - Chronic: dryers scale or become lichenified
Regional Eczema
- Ear eczema
- Eyelid Dermatitis
- Nipple Eczema
- Hand Eczema
- Diaper Dermatitis
- Infectious Eczematoid Dermatitis
- Juvenile plantar dermatosis

Ear Eczema
- Involve helix, postauricular fold, external canal
- Often manifestation of seborrheic dermatitis or allergic contact dermatitis
- Secondary bacterial colonization or infection are common
  - Staph, strep, pseudomonas
- Earlobe dermatitis is pathognomonic of nickle allergy in women with earring
- Treatment:
  - Removal of offending agents
  - Topical steroid

Eyelid Dermatitis
- Commonly related to atopic dermatitis or allergic dermatitis
- Upper eyelids involvement
  - Allergic contact dermatitis
- Both upper and lower eyelids
  - Atopic dermatitis
- One eye involvement
  - Nail polish
**Breast eczema**
- Affect the nipples, areolae, or surrounding skin
- Present with moist type with oozing and crust, painful fissure, especially in nursing mother
- Breast eczema has persisted for more than 3 months, unilateral => need biopsy to rule out Paget's disease
- Treatment:
  - Topical or intralesional corticosteroid

**Nipple Eczema**

**Hand Eczema**
- Represents a major occupational problem
- Frequently miss work and change occupations
- Involve wet work environment, low humidity
  - hair dresser – glyceryl monothioglycolate, ammonium persulfate
  - Cement worker - chromate
  - Preservative allergy – isothiazolinones, formaldehde
Acute Vesiculobullous Hand Eczema
- Presents with severe, sudden outbreaks of intensely pruritic vesicles, symmetrical
- Lesions are macroscopic, deep-seated multilocular vesicles resembling tapioca on the sides of fingers, palms, soles
- Resolve spontaneously over several weeks
- DDx: bullous tinea, Id reaction

Chronic Vesiculobullous Hand Eczema
- Presents with hyperkeratotic, scaling, and fissured, 1-2 mm pruritic vesicles
- Female 3:1 male
Hyperkeratotic Hand Eczema

- Presents as hyperkeratotic, fissure-prone, erythematous areas of middle or proximal palm
- Male 2:1 female

Treatment

- Barrier
  - Vinyl gloves, rubber gloves
- Moisturizer
  - Ointment is preferred due to low risk of contact sensitivity
- Topical Steroid
  - Superpotent and potent steroid are first line
  - Single occlusion at night is better than multiple daytime tx
- Calcineurin inhibitors
- Systemic Steroid
  - Usually results in dramatic improvement but rapidly relapse
- Phototherapy
  - UVAs alone, UVB, Narrow-band UVB or soak PUVA can be effective
Atopic Dermatitis

- Drugs on the Horizon
  - PDE-4 Inhibitor, a
    - Phase 2 studies in 2013
    - Promising results for mild/moderate AD adolescent patients
  - No evidence of toxicity
  - Dupilumab
    - Human monoclonal antibody
    - IL-4/13 blocker
    - Promising results in adults with moderate to severe AD
      - Halved the severity of 86% of patients
      - Cleared 40%
  - Topical Efoog
    - Statistical improvement over placebo at 12 weeks
    - Safe and well-tolerated

Diaper (Napkin) Dermatitis

- High prevalence is between 6-12 months of age or adults with urinary or fecal incontinence
- Presents with erythematous, papulovesicular dermatitis distributed over the lower abdomen, genitals, thighs, and convex surfaces of buttocks
- The folds remain unaffected to differentiate from intertrigo, inverse psoriasis, candidiasis

Diaper Dermatitis

- Candida is frequently a secondary infection with typical satellite erythematous lesions
- Jacquet’s erosive diaper dermatitis
  - Punched-out ulcers or erosions with elevated border
- Granuloma gluteal infantum
  - Violaceous plaques and nodules
Treatment

- Prevention is best treatment
- Superabsorbent gel diaper
- Cloth diaper and regular disposable diaper
- Zinc oxide paste to protect the skin
- Application of mixture of equal parts Nystatin and 1% hydrocortisone to offer both antifungal activity and occlusive protective barrier from urine and stool

Id Reaction

- Patient presents with eczematous dermatitis 2nd to variety of infectious disorders
- Vesicular Id reactions of hand in response to an inflammatory tinea of the feet
- Nummular eczematous lesions or pityriasis rosea-like lesions may occur in patients with louse infestation
- Frequently unresponsive to cortisone therapy; but clear when infection is treated

Juvenile Plantar Dermatosis

- Presents as patchy, symmetrical, smooth, red macules on base or medial surface of great toe in children aged 3 to puberty
- Lesions evolve into red scaling patches involving weight-bearing and frictional areas of feet; but spared toe webs and arches
- Virtually always resolve after puberty
- Treatment:
  - Avoidance of maceration
  - Eliminate offending agents
  - Topical steroid has limited value
Juvenile plantar dermatosis

Xerotic Eczema (Eczema Craquele)
- Aka winter itch, nummular eczema
- Present as erythematous patch covered with adherent scale on anterior shins, extensor arms and flank
- Most common cause of pruritus in older individuals
- Treatment:
  - Short bath, use of bath oils
  - White petrolatum and emollients containing urea or lactic acid
**Nummular Eczema**

-Presents as discrete, coin-shaped, erythematous, and crusted patches on lower legs, dorsal of hands or extensor surface of arms

-Pruritic is usually severe, paroxysmal, and nocturnal

-Treatment:
  - Simple soaking and greasing with occlusive ointment
  - Potent or superpotent topical steroid
  - Sedating antihistamine at bedtime
  - Treat secondary infection

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**References**

- **Dermatology.** Bologna et. al. 2003.
- **Pediatric Dermatology.** Schachner et. al. 2011.