Overview

- Mediators
- Etiologies
- Physical Urticaria
- Chronic Idiopathic Urticaria
- Hereditary Urticaria Syndromes
- Urticarial Vasculitis
- Angioedema syndromes
Potential Mediators in Urticaria

- **Histamine**
  - Vasodilation, vascular permeability

- **Substance P**
  - Released by type C fibers by antidromic conduction
  - Vasodilator

- **PGD2**
  - Vasodilator

- **LTC4/LTD4**
  - Vascular permeability

- **?PAF**
  - Vascular permeability

- **C3a/C5a**

- **Bradykinin**
  - Vasodilation
  - Vascular permeability

- **Histamine releasing Factor (HRF)/β-chemokine**

- **Thrombin**
Urticaria & Angioedema Etiologies

- Idiopathic
- Medications
  - Acute > chronic
- Stings (acute)
- Foods or additives (acute)
- Inhalation (acute)
- Infection
- Physical urticarias

- Neoplasms
- Connective tissue disease
- Endocrine
- Urticarial vasculitis
- Contact (acute)
- Transfusion reactions
- Hereditary Disorders
Connective Tissue Disease and Urticaria

- SLE
  - < 10% patients
  - Most urticarial vasculitis
- Sjogren’s
  - Majority are urticarial vasculitis
- Cryoglobulinemia
  - Hepatitis C
- Rheumatoid Arthritis?
Neoplasms and Urticaria

- Uncommon cause
  - B-cell Lymphomas and Hodkins
  - Carcinomas
    - Lung, colorectal, liver

- Schnitzler Syndrome
  - IgM monoclonal paraproteinemia
  - Nonpruritic urticaria (later may be pruritic)
  - Intermittent spiking fever
  - Arthralgias, bone pain, hyperostosis
  - Lymphadenopathy
    - anakinra effective
Parasites and Urticaria

- Helminths
  - Ascaris, Ancylostoma, Strongyloides, Filaria, Echinococcus, Schistosoma, Trichinella, Toxocara, and Fasciola

- Associated with eosinophilia
Physical Urticarias

Prime Board Exam Fodder
Cold Urticaria

- Urticaria on cold-exposed areas of the body
- Systemic reactions can occur with shock
  - Avoid swimming in lakes
- Diagnosis
  - Ice cube test
- "Drug of choice"
  - Cyproheptadine
  - Other antihistamines also work
Mechanisms of Idiopathic Cold Urticaria

- Histamine peaks 4-8 minutes after cold exposure
- Antibody mediated and passively transferred
  - IgE, IgG, IgM
- Other mediators
  - NCF, PAF, PGD2, TNF-a
Cold Urticaria Syndromes

- Idiopathic (most common)
- Secondary forms
  - Cold-dependent immunoglobulin diseases
    - Cryoglobulinemia
    - Cold agglutinin disease
    - Cryofibrinogenemia
    - Paroxysmal cold hemoglobinuria
    - Cold hemolysis
- Delayed Cold Urticaria
  - Swelling 9-18 hrs after cold exposure
  - Not passively transferred
**Cold Urticaria Syndromes -2**

- Localized cold urticaria
  - Certain areas of body urticate with cold exposure
  - Predisposing factors
    - Cold injury
    - Immunotherapy injection sites
    - Insect bites

- Localized cold reflex urticaria
  - Ice cube test positive but only in the vicinity of the contact site
Ice Cube Test Negative Cold Urticaria

- Cold-induced cholinergic urticaria
  - Exercise in cold air causes urticaria resembling cholinergic urticaria
  - Requires systemic cold exposure
- Systemic cold urticaria
  - Generalized hives with systemic cold exposure
  - Unrelated to exercise
- Cold-dependent dermographism
  - Accentuated hive formation if skin scratched and then chilled
Local Heat Urticaria

- Very rare
- Test tube of water @ 44 °C to arm for 5 minutes
  - Hive forms few minutes later
- Histamine and NCF released
Cholinergic urticaria

- Occurs primarily in teenagers and young adults
- Pruritic, small macules and papules occur in response to heat, exercise, or emotional stress
  - May have other cholinergic symptoms
    - Lacrimation, salivation, diarrhea
  - May occur with wheezing
  - May occur without visible skin lesions (cholinergic pruritus)
Cholinergic urticaria

Pathophysiologic Mechanisms

- Neurogenic reflex
  - Placing hand in warm water with proximal tourniquet does not cause local hives
  - Removal of tourniquet leads to generalized eruption
- Central perception of temperature change
- Autologous sweat sensitivity
  - Sweat may cause basophil degranulation in sensitive subjects
Cholinergic Urticaria subtypes

- Non-follicular
  - Most common
  - Hypersensitivity to autologous sweat
  - Satellite wheals to acetylcholine skin test
  - Negative ASST (autologous serum skin test)

- Follicular
  - Follicular wheals
  - Weak to no response to autologous sweat
  - No satellite wheals to acetylcholine
  - Positive ASST

Cholinergic Urticaria

- Diagnostic testing
  - Challenge by exercise or hot water (44ºC)
  - Methacholine skin testing
    - Poor specificity and sensitivity
  - Autologous sweat skin testing
    - Positive in non-follicular subtype

- Drug of choice
  - hydroxyzine
Cholinergic Urticaria with Hypotension

- Rare reports of patients with cholinergic urticaria with recurrent hypotension
  - Increase in core body temperature > 0.7 °C with warming blankets or submersion in warm water causes urticaria, histamine release and anaphylactic symptoms
- Patients with exercise-induced anaphylaxis will not react to passive heating
Delayed Pressure Urticaria (Angioedema)

- Symptoms develop 4-6 hrs after pressure stimulus
  - Hands, feet, buttocks
- Usually associated with non-pressure induced chronic urticaria
- “Sandbag” test
  - 5-15 lb weight applied over forearm, shoulder, thigh for 10-20 minutes
- Usually unresponsive to antihistamines
- Corticosteroids may be required
Dermographism

- Very common - affects 2-5% of population
- Small fraction of these patients will seek treatment
- Stroking of the skin results in linear wheals which may persist as long as 30 minutes
  - patients may complain of generalized pruritus or “skin crawling”
- Passive-transfer studies suggest an IgE-mediated reaction
- Associations
  - Penicillin therapy
  - Contact dermatitis
  - Other physical urticarias
  - mastocytosis
Solar Urticaria

- Rare disorder
- Brief exposure to light causes urticaria within 1-3 minutes
  - Lesions last 1-3 hrs
- Most patients in 3rd and 4th decade of life
Solar Urticaria Types

- **Type I & IV**
  - May be passively transferred
  - Type I protected by ordinary window glass

- **Type VI**
  - Erythropoietic protoporphyria
    - Protoporphyrin IX acts as a photosensitizer
    - Porphyrin in urine is normal
    - Protoporphyrin and coproporphyrin in feces are increased

- **Type II, III, V**
  - mechanism unknown
Aquagenic Urticaria

- Rare form of urticaria
- Patients develop small wheals with contact with water independent of temperature
- Tap/distilled water compress applied to the skin
## Tests For Physical Urticaria

<table>
<thead>
<tr>
<th>Type</th>
<th>Test Description</th>
</tr>
</thead>
<tbody>
<tr>
<td>Cold</td>
<td>Ice cube test</td>
</tr>
<tr>
<td>Localized Heat</td>
<td>Test tube water 44ºC</td>
</tr>
<tr>
<td>Cholinergic</td>
<td>Exercise for 15-20 min.</td>
</tr>
<tr>
<td></td>
<td>Leg immersion in 44ºC bath</td>
</tr>
<tr>
<td>Delayed Pressure</td>
<td>Sand bag test: 15 lb weight for 15 minutes</td>
</tr>
<tr>
<td>Dermographism</td>
<td>Stroking skin</td>
</tr>
<tr>
<td>Solar</td>
<td>Specific wavelength light exposure</td>
</tr>
<tr>
<td>Aquagenic</td>
<td>Water compress</td>
</tr>
<tr>
<td>Vibratory</td>
<td>Vortex for 4 minutes</td>
</tr>
</tbody>
</table>
Physical Urticaria: Passive Transfer by Serum

- **Cold**
  - IgE, IgM, IgG, cryoglobulins
- **Solar Type I & IV**
  - IgE ?
- **Dermographism**
  - IgE
Chronic Autoimmune Urticaria

- 30-40% CIU autoimmune cause
- Thyroid autoantibodies > 20% of CU pts
  - anti-thyroid peroxidase > anti-thyroglobulin Ab
- IgG or IgM antibodies against high-affinity IgE receptor
  - α chain
  - Rarely anti-IgE antibodies
- C5a augments histamine release by IgG anti-α antibodies
- Detected through autologous serum skin test and basophil histamine release assays
Chronic Idiopathic Urticaria

- After exclusion of acute urticaria and physical urticarias, identifiable etiologies may be found in < 2% cases according to Kaplan

- Skin biopsy
  - Nonnecrotizing perivascular mononuclear cell infiltrate
  - Primarily lymphocytes
  - Increased mast cells in some but not all studies
  - Similar to late-phase allergic reactions except
    - Less basophils, variable eosinophils, prominent monocytes and lymphocytes
Hereditary Urticaria & AE Syndromes

- Cryoprinopathies
- Hereditary Vibratory Angioedema
- Factor I Deficiency
- Estrogen Dependent/Associated Inherited Angioedema
- Hereditary Angioedema
Cryopyrinopathies

- *C1AS1* gene encodes the protein cryopyrin (NALP3)
- Cryopyrin is a key component of the inflammasome
- Inflammasome is an intracellular complex that senses “danger” signals and activates IL-1β
- Mutations in *C1AS1* cause
  - Familial cold autoinflammatory syndrome
  - Muckle-Wells syndrome
  - NOMID
- All autosomal dominant
“Familial Cold Urticaria”

Familial Cold Autoinflammatory Syndrome (FCAS)

Mutations in cold-induced autoinflammatory syndrome 1 gene (*CIAS1*)

- Symptoms upon exposure to cold
  - Burning papular lesions
  - Fever, chills
  - Arthralgias, myalgias, conjunctivitis, headache, leukocytosis
  - Ice cube test negative
Muckle-Wells Syndrome

- CIAS1 gene mutations
- Familial urticaria
  - urticarial vasculitis and cold urticaria reported
- Renal amyloidosis
- Deafness
- Polyarthralgias
NOMID

- Neonatal-onset multisystem inflammatory disease (NOMID)
  - a.k.a. chronic infantile neurologic cutaneous articular syndrome (CINCA)
- Most children have mutations in *C1AS1*
- Clinical Features
  - Urticaria-like rash within 1st 6 weeks of life
  - **Bony overgrowth**
  - CNS manifestations
    - **Chronic aseptic meningitis, mental retardation, cerebral atrophy, chronic papilledema, SNHL, etc.**
NOMID

- Laboratory
  - ↑ WBC, ↑ amyloid A, ↑ ESR
- Therapy
  - IL-1 receptor antagonist (anakinra)

Spectrum of Cryopyrinopathies

Autoinflammatory Syndromes

- Cryoprinopathies
- Familial Mediterranean Fever
- Hyper IgD syndrome
- TRAPS
- Blau syndrome
- Chrohn’s
  - Non-Mendelian inheritance
  - Recurrent fevers not a feature
Systemic Autoinflammatory Disorders

- Familial Mediterranean Fever
  - Autosomal recessive
  - Pyrin mutations
  - Erysipeloid erythema, abdominal pain, arthritis, pleuritis, amyloidosis

- Hyper IgD syndrome
  - Autosomal recessive
  - Mevalonate kinase mutations; ↑ IgD
  - Maculopapular rash, abdominal pain, cervical adenitis
Systemic Autoinflammatory Disorders

- TRAPS (TNF receptor associated periodic syndrome)
  - **TNFRSF1A** mutations; autosomal dominant
  - fever, abdominal pain, pleurisy, migrating erythema, periorbital edema, conjunctivitis, amyloidosis

- Blau Syndrome
  - **CARD15 (NOD2)** mutation; autosomal dominant
  - Fever, granulomatous arthritis, uveitis, erythematous papular rash, camptodactyly
Hereditary Vibratory Angioedema

- Autosomal dominant
  - Nonfamilial cases also reported
- Pruritus and swelling within minutes of vibratory stimuli
- Diagnosed by using a lab vortex for 4 minutes
- Histamine elevated after vibratory stimulus
- Antihistamines partially beneficial
Factor I Deficiency (C3b inactivator)

- Rare disorder
- Autosomal recessive
- May present with urticaria
- Depressed C3 levels
  - May have liberation of C3a anaphylatoxin
Urticaria Pharmacotherapy

- Antihistamines
  - $H_1$ receptor antagonists
  - $H_2$ receptor antagonists
- Leukotriene antagonists
- Oral corticosteroids
- Cyclosporine, tacrolimus
- Others
  - omalizumab, dapsone, hydroxychloroquine, colchicine, sulfasalazine, IVIG, androgens, methotrexate, cyclophosphamide, androgens, gold, phototherapy, plasmapheresis
Prevalence ~5% CIU
Female predominance
Peak incidence 4\textsuperscript{th} decade
Histopathology can be indistinguishable from leukocytoclastic vasculitis (palpable purpura)
- Leukocytoclasis
- Vessel wall damage
- +/- Fibrin deposits or RBC extravasation

Immunofluorescence
- Igs, Complement, fibrin within vessel wall

Clinical Features of UV

- Urticaria description
  - Painful, tender, burning or pruritic
- Duration of lesions
  - 24-72 hrs
- Lesions resolve with purpura or hyperpigmentation
Hypocomplementemmetic urticarial vasculitis syndrome (HUFS)

- More serious and systemic form of UV
  - Death due to vasculitis rare
- Urticaria and hypocomplementemia

- Associated features
  - Angloedema (50%)
  - Obstructive lung disease (50%)
  - Uveitis, episcleritis (30%)
  - Arthralgia, arthritis
  - Mild glomerulonephritis
  - Recurrent abdominal pain
  - Cardiac disease (rare)
  - Neurologic problems (e.g. pseudotumor cerebri)

- All of above features can be seen with normocomplementemmetic UV but are more common with HUFS
Laboratories in HUVS

- Hypocomplementememia
  - ↓ C3 or C4
  - ↓↓ C1q
- Anti C1q antibodies (most all patients)
  - Relatively specific for HUVS and SLE
- 50% ANA +
  - dsDNA −
- ↑ ESR
Urticarial Vasculitis

- **Etiology**
  - Idiopathic most common
  - SLE, Sjogrens
  - Numerous other rare causes

- **Treatment**
  - Antihistamines (help with pruritus)
  - Dapsone, colchicine, hydroxychloroquine, indomethacin
  - Corticosteroids
  - Azathioprine, methotrexate, cyclosporine, cyclophosphamide, mycophenolate

- **Prognosis**
  - Average duration 3-4 years
  - UV typically has benign course
  - HUVS has a worse prognosis
    - COPD common cause of morbidity and mortality
ACE-I Angioedema

- Occurs in 0.1-0.7%
  - more common in African-Americans
- Usually delayed in onset
  - Mean 1.8 yrs (Malde 2007)
- Likely des-Arg bradykinin induced
  - ACE (kinase II) activates bradykinin and angiotensin I
- Usually tolerate ARBs but case reports of AE with ARBs too
Estrogen Dependent/Associated Inherited Angioedema (aka HAE type III)

- Extremely rare
- Women with recurrent AE episodes
  - Autosomal dominant?
- Normal C1-INH antigenic and function levels
- No mutations identified in C-INH gene
- Estrogen Dependent
  - AE only during pregnancy or supplemental estrogen
- Estrogen Associated
  - AE exacerbated by estrogen but occurs at other times
C1-INH belongs to family of serine protease inhibitors (serpins) and inhibits:

- C1s and C1r (classical pathway)
- Mannin-binding lectin-associated serine proteases (MASPs)
- FXIa (intrinsic pathway of coagulation)
- FXIIa and kallikrein (contact system)
- Weakly inhibits
  - Thrombin, plasmin, tissue-type plasminogen activator

C1-INH gene
- Chromosome 11
- > 150 mutations identified over entire length of coding sequence
Hereditary Angioedema

- Clinical characteristics
  - Autosomal dominant
  - Acute attacks
    - Symptoms progress over 24-48 hours and resolve over the next 48 hours
    - angioedema of extremities, face, throat
    - abdominal pain, nausea, vomiting, diarrhea
    - no urticaria or pruritus
    - Symptoms not helped by antihistamines
    - May be precipitated by trauma
      - dental work
  - Hormonal effects variable
Hereditary Angioedema

- Associated conditions
  - SLE and autoimmune disorders (?)
  - Other cutaneous findings (26% in survey by Frank et al)
    - Erythematous mottling
    - Erythema multiforme
    - Erythema marginatum
Hereditary Angioedema

- **Type I**
  - ~85% patients with C1-INH deficiency
  - Defective expression of 1 allele of C1-INH gene
  - Low C1 INH antigenic and function

- **Type II**
  - ~15% patients with C1-INH deficiency
  - Dysfunctional mutant protein
  - C1-INH antigenic levels nl or high, functional levels decreased
Hereditary Angioedema Pathophysiology

- **Bradykinin** most likely mediator involved
  - Evidence in both HAE and AAE
- C2-kinin evidence weak
Acquired Angioedema (AAE)

- Clinical presentation similar to HAE except not hereditary and later onset (4th decade of life or later)

- Increased consumption of C1-INH and hyperactivation of classical complement
  - Consumption by neoplastic lymphatic tissue
  - Autoantibodies to C1-INH impair C1-INH function
    - May enhance cleavage to non-functional but antigenic protein
    - In this case C1-INH levels are normal
Acquired Angioedema (AAE)

- "Type I" (paraneoplastic)
  - B cell lymphoproliferative disease
  - MGUS (monoclonal gammopathy of unknown significance)
    - May also have autoantibody to C1-INH at some time in course of disease

- "Type II" (autoimmune)
  - Otherwise healthy
  - Autoantibody to C1-INH always present
### Laboratories in Hereditary and Acquired Angioedemas

<table>
<thead>
<tr>
<th></th>
<th>C1-INH level</th>
<th>C1-INH function</th>
<th>C1q</th>
<th>C4</th>
<th>C3</th>
</tr>
</thead>
<tbody>
<tr>
<td>HAE-I</td>
<td>↓</td>
<td>↓</td>
<td>N</td>
<td>↓</td>
<td>N</td>
</tr>
<tr>
<td>HAE-II</td>
<td>N or ↑</td>
<td>↓</td>
<td>N</td>
<td>↓</td>
<td>N</td>
</tr>
<tr>
<td>EDIAE</td>
<td>N</td>
<td>N</td>
<td>N</td>
<td>N</td>
<td>N</td>
</tr>
<tr>
<td>AAE-I</td>
<td>↓</td>
<td>↓</td>
<td>↓</td>
<td>↓</td>
<td>N or ↓</td>
</tr>
<tr>
<td>AAE-II</td>
<td>↓ or N</td>
<td>↓</td>
<td>↓ or N</td>
<td>↓</td>
<td>N or ↓</td>
</tr>
</tbody>
</table>

**EDIAE:** Estrogen-dependent inherited angioedema
Treatment Options for C1-INH Deficiencies

**Acute AE**
- Basics
  - Airway management
  - Hydration
  - Pain relief
- C1-INH concentrate
- Anti-fibrinolytics (+/-)
- FFP (?)

**Short-term prophylaxis**
- Androgens 3-5 days prior
- FFP, C1-INH concentrate, anti-fibrinolytics

**Long-term prophylaxis**
- Attenuated Androgens
  - Danazol, stanozolol, oxandrolone
- Antifibrinolytics
  - $\varepsilon$-aminocaproic acis (Amicar)
  - Tranexamic acid
- C1-INH concentrate

**Future therapies**
- r-C1-INH
- Bradykinin receptor antagonist
- Kallikrein inhibitors
Issues with Therapies for HAE

- Attenuated androgens
  - Adverse effects
    - Hepatotoxicity (rarely liver carcinoma)
    - Weight gain, menstrual irregularities, ↓ libido, virilization, acne, myalgias, fatigue, headache, hypertension
  - Contraindications
    - Pregnancy, lactation, childhood*, prostate CA

- Antifibrinolytics
  - Thrombosis, postural hypotension, myalgias, myositis
Therapy for AAE

- Treatment of underlying disease
  - May result in biochemical/clinical remission of AAE

- Androgens
  - AAE frequently resistant

- Antifibrinolytics
  - May be preferred over androgens

- C1-INH concentrate
  - May require higher doses and be more resistant to treat than HAE