URTICARIA

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Objectives

• Give a diagnosis of urticaria
• To recognize the cause of acute, chronic urticaria and angioedma
• The know the provocative challenges for physical urticaria
• Give an appropriate investigation
• Give proper management
Urticaria

• Wheals and flare reaction: pruritus (itch)

Wheal- localized intracutaneous edema
Flare- surrounding area of erythema

• AS A RULE: individual lesions come and go rapidly, within 24 hours
• Leaves no trace
Angioedema

- Deep swelling of the dermis or subcutaneous tissue of the skin or mucosa
- Painful, not well defined
- The lesions often last for 2 to 3 days
Cutaneous mast cell

Release histamine in response to

• compound 48/80
• C5a
• morphine
• codeine
• substance P (SP)
• vasoactive intestinal peptide (VIP)
• somatostatin
Vascular permeability in skin
• H1 histamine receptors- 85%
• H2 histamine receptors- 15%
Urticaria

Ordinary urticaria
• Acute urticaria (<6wk)
• Chronic urticaria (>6wk)

Urticarial lesion
• Cutaneous disease
• Systemic disease
Main features distinguishing common urticaria from other urticarial lesions

<table>
<thead>
<tr>
<th>Common urticaria</th>
<th>Other urticarial lesions</th>
</tr>
</thead>
<tbody>
<tr>
<td>Typical wheals:</td>
<td>Atypical wheals:</td>
</tr>
<tr>
<td>• Erythematous, edematous lesions</td>
<td>• Infiltrated plaques</td>
</tr>
<tr>
<td>• Transient &lt; 24-36 hrs</td>
<td>• Persistent &gt; 24-36 hrs</td>
</tr>
<tr>
<td>• Asymmetrical distribution</td>
<td>• Symmetrical distribution</td>
</tr>
<tr>
<td>• Complete resolution</td>
<td>• Resolution with sighs eg hypo/hyperpigmentation, scarring</td>
</tr>
<tr>
<td>No other primary lesions</td>
<td>No other primary lesions</td>
</tr>
<tr>
<td>Pruritic</td>
<td>Pruritic</td>
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<tr>
<td>+/- angioedema</td>
<td>Not associated with angioedema</td>
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</tbody>
</table>
Acute urticaria

- Wheal and flare of less than 6 weeks duration
- Children - infections and food
- Adults - medications

Causes of acute urticaria:

- Idiopathic: 50%
- Upper respiratory tract infections: 40%
- Drugs: 9%
- Foods: 1%
Acute Urticaria

- Common in both children and adults
- Self-limiting condition
- Prevalence of about 15% to 20% in the general population
- Complete resolution within 3 weeks in more than 90% of cases
Acute urticaria
Acute Urticaria

Prick Test

Allergen solution is placed on skin

Positive test: Skin is red and itchy
Acute Urticaria

Prick Test

- Implication for food and inhalant material
- Very little role for diagnosis of chronic urticaria
Food Allergy

• 20-60% with acute urticaria
• <2% with chronic urticaria

Double-blinded placebo-controlled food challenge is the gold standard

Skin test false negativity due to instability of allergen in food extract used for skin testing
Acute Urticaria

Drug induced urticaria
Management of Acute Urticaria

• Identify and eliminate endogenous and exogenous cause

• Advice that it takes several weeks for the lesions to go away completely

• Other laboratory investigation eg CBC, complete metabolic panel, thyroid testing, UA NOT NECESSARY
Management of Acute Urticaria

• Specific Treatment

  Nonsedating antihistamine
  Sedating antihistamines is the mainstay

  Corticosteroids 60-80 mg/day for 3 days
  then taper 5-10 mg/day

  Epinephrine (severe, angioedema)
Case 3

A 34 year-old woman with hives daily for 4 months
She occasionally has associated upper lip swelling but denies dyspnea or throat swelling
Review of systemic symptoms are otherwise negative

Diagnosis?
Chronic urticaria

Recurrent at least twice / week for > 6 weeks

Urticaria and angioedema (40%)
Uriticaria alone (40%)
Angioedema alone (20%)

Prevalence of 0.5% to 3% in the general population
Common in 3rd and 4th decades, rare in children
Not associated with food, pollens, dyes ect.
Bad news.......May last for years
Chronic urticaria

Persist for months or years

- 50% of pt. free of lesions within 1 year
- 65% “ 3 years
- 85% “ 5 years
- <5% of pt. lesions last >10 years

- Angioedema-25% clear in 1 year
presence of autoantibodies to FceRla or to IgE
presence of autoantibodies to FCεRI or to IgE
**FIGURE 37-1** Schematic diagram of the activation of cutaneous mast cells by immunoglobulin G (IgG) antireceptor antibody, followed by activation of complement, release of C5a, and augmentation of mast cell release.
Chronic autoimmune urticaria

- Autoimmune thyroid disease
- Vitiligo
- Insulin dependent diabetes
- Rheumatoid arthritis
- Pernicious anemia
- HLA-DR4, HLA-DQ8
Chronic autoimmune urticaria: Methods of detecting autoantibody

- Basophil histamine release assay is the Gold Standard
- Direct immunoassays
  - Western blotting
  - Immunoprecipitation
  - ELISA
  - Flow cytometry
- ASST (sensitivity 70%, specificity 80%)
Chronic Autoimmune Urticaria

Autologous Serum Skin Test

Response within 30 mins
At least 1.5 mm
presence of autoantibodies to FceR1a or to IgE
Pseudoallergic reaction

- Direct action of the substance on mast cells
  - opiates, radiocontrast media
- Interference of drugs
  - aspirin and other NSAIDs
  - inhibit cyclooxygenase (COX) 1 and 2 with arachidonic acid metabolism
  - increased synthesis of cysteinyl leukotrienes
  - induces vasodilatation and edema
presence of autoantibodies to FceR1a or to IgE

Helicobacter pylori gastritis
Hepatitis B,C
Parasite
Fungus: dermatophyte, C albicans, Giardia, Trichomonas
Inducible urticaria

Types of physical urticaria

Individual lesions last < 2 hours

• Cold urticaria
• Cholinergic urticaria
• Dermographism
• Heat contact urticaria
• Aquagenic urticaria
• Solar urticaria
• Vibratory urticaria

Lesions last > 2 hours

• Delay pressure urticaria
Inducible urticaria

Urticaria due to mechanical stimuli
Inducible urticaria

Urticaria due to mechanical stimuli
Inducible urticaria

Dermographism

- Most common form of physical urticaria
- Linear wheal with a flare where the skin is briskly stroked with a firm object
- 1.5 - 4.2% in the general population
- No association with systemic disease, atopy, food allergy or autoimmunity.
- Mean duration 5-7 years
Delayed dermographism

- Lesions develop 3 to 6 hours after stimulation, either with or without an immediate reaction, and last 24 to 48 hours.
- May be associated with delayed pressure urticaria
Inducible urticaria

Cholinergic Urticaria
Cholinergic urticaria

- Develops after an increase in core body temperature
- Multiple transient papular wheals 2–3 mm surrounded by flare.
- Occur within 15 minutes
- More frequently in young adults with an atopic tendency
- The intracutaneous injection of cholinergic agents, methacholine chloride, produces a wheal with satellite lesions in 1/3 of patients.
Inducible urticaria

Heat contact urticaria

- Rarest from of urticaria
- Within minutes of contact with heat from any source
- Systemic symptoms may occur if urticaria is extensive
Inducible Urticaria
Cold Urticaria

Positive wheal at the test site within 20-30 minutes
Cold urticaria

• Whealing occurs within minutes of rewarming after cold exposure.

*Primary cold contact urticaria*
• Follow respiratory infections, or arthropod bites or stings, HIV infection
• Cold baths and swimming should be avoided.

*Secondary cold contact urticaria*
• Cryoglobulinemia or cryofibrinogenemia
• Associated with manifestations such as Raynaud’s phenomenon or purpura
• May have underlying HBV or HCV infections, lymphoproliferative disease or infectious mononucleosis.
### Inducible urticaria

**Exercise-induced anaphylaxis (EIA)**

**Food- and exercise-induced anaphylaxis (FEIA)**
- Angioedema and/or anaphylaxis occur within minutes of exercise if it follows either prior ingestion of a specific food (e.g. wheat), or within 4 hours of a heavy meal.
- Due to priming of the mast cell by prior exposure to an allergen, or to an unknown mechanism.

**Exercise-induced anaphylaxis (EIA)**
- Produced by exercise
- Not associated with increase in core temperature like cholinergic urticaria
<table>
<thead>
<tr>
<th>Inducible urticaria</th>
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<tbody>
<tr>
<td>Adrenergic urticaria</td>
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- Presence of blanched vasoconstricted skin surrounding small pink wheals
- Induced by sudden stress
- The lesions can be reproduced by intradermal injections of norepinephrine.
Inducible urticaria

Solar Urticaria

Phototest

Visible light: immediately after test

Wheal and erythematous flare on test site
Solar urticaria

- Itching and whealing occur within minutes of exposure to UV or visible wavelengths.
- Solar radiation may penetrate light clothing.
- Wheals last < 1 hr
- Headache and syncope can accompany severe reactions.
Inducible urticaria
Aquagenic urticaria

• Contact with water of any temperature induces smalll wheals urticarial eruption
• Occur most frequently on the upper part of the body
• Last for < 1 hr.
• Must be differentiated from aquagenic pruritus (HD, PV, MDS)
Inducible urticaria

Contact urticaria

- Development of urticaria at the site of contact with skin or mucosa
- Percutaneous or mucosal penetration of the urticant may have distant effects, including acute urticaria or even anaphylaxis
<table>
<thead>
<tr>
<th>Immunologic</th>
<th>Non-immunologic</th>
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<tbody>
<tr>
<td><strong>IgE-independent</strong></td>
<td><strong>Direct effects of urticants on blood vessels</strong></td>
</tr>
<tr>
<td>– Grass</td>
<td>– Sorbic acid</td>
</tr>
<tr>
<td>– Animals</td>
<td>– Benzoic acid</td>
</tr>
<tr>
<td>– Foods</td>
<td>– Cinnamic aldehyde (PGD2)</td>
</tr>
<tr>
<td>– Latex</td>
<td>– Nettle stings (histamine, acetylcholine, serotonin)</td>
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<tr>
<td></td>
<td>– Dimethylsulfoxide</td>
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<tr>
<td></td>
<td>– Cobalt chloride</td>
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<td><strong>Inhibited by NSAIDs.</strong></td>
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Inducible urticaria

Vibratory urticaria

- Very rare form of urticaria

- Vibratory stimulus induces localized swelling and erythema within minutes, lasting 30 minutes.
Vibratory angioedema

- The acquired form
  - milder
  - associated with DPU and symptomatic dermographism.
- The familial form
  - dominantly inherited
  - intense vibratory stimuli may induce generalized erythema and headache
Physical Urticaria

Delayed pressure urticaria
Urticarial vasculitis

- Resemble urticaria
- Histologically show evidence of leukocytoclastic vasculitis
- Lesions persist for >24 hours
- Burn, painful with pruritus
- Resolve with residual purpura
- Angioedema up to 40% of patients
- Arthralgias in 50%
Angioedema without Wheals

• Idiopathic
• Drug reaction:
  – Aspirin, NSAIDs
  – ACE inhibitor: African-American polymorphism enzymes catabolize bradykinin contraindicated in pt. with history of angioedema
• C1 esterase inh deficiency
Direct mast cell degranulation

• Radiocontrast media
• Opiate
• Analgesics
• Polymyxin B
• Curare
• D- tubocurarine
**Inducible Urticarias**

- Dermatographism
- Cold
- Cholinergic
- Local heat
- Delayed pressure
- Solar
- Aquagenic
- Vibratory

- Stroke with tongue blade (36g/mm²)
- Ice cube in thin bag 5 minutes
- Exercise til sweat, hot bath 42C, 10 min
- 44 C 5 minutes
- Sandbags 15 lbs 15 minutes
- Specific wavelengths
- 35 C water compress
- Vortex 4 minutes
Chronic Autoimmune Urticaria
Autologous Serum Skin Test

Response within 30 mins
At least 1.5 mm

histamine
Investigations of Chronic Urticaria

Exclude physical urticaria

Exclude urticarial vasculitis

Exclude thyroid disease by screening thyroid antibody test
  • If positive: perform thyroid function test
  • Positive result strengthens the likelihood of an underlying autoimmune process
Investigations of Chronic Urticaria

WBC count for eosinophilia

Stool exam requested in the presence of eosinophilia

Investigate for autoimmune urticaria
Management of Chronic Urticaria

• Identify and eliminate endogenous and exogenous cause

• Advice that it takes months to years for the lesions to go away completely
Laboratory examinations

- CBC, Stool exam, HBsAg, CXR
- Antinuclear antibodies
- ESR, C-reactive protein
- Complement
- Antithyroperoxidase antibodies and thyroid function tests
- Autologous serum or plasma skin test
What would be your first prescription?

a) Topical steroids
b) Oral steroids
c) Topical antihistamines
d) Oral antihistamines
H₁ antihistamine

• Inverse agonists
  “agent that binds to the same receptor as an agonist but induces a pharmacological response opposite to that agonist”

• Combine and stabilize the inactive conformation of histamine receptor
Histamine has affinity for the active state and shifts the equilibrium toward the active state.

Estelle F et al. J Allergy Clin Immunol;128:1139
Antihistamine has preferential affinity for the inactive state, and shifts the equilibrium toward the inactive state.

Estelle F et al. J Allergy Clin Immunol;128:1139
Beneficial effects of H1-antihistamines

- Directly interfere H1 receptor on sensory neuron, small blood vessels esp post-capillary venules
- Down regulates inflammation: ↓NF-κB
Wheal and flare suppression correlate(s) best with

(a. H₁ antihistamine receptor occupancy of unbound drug
b. H₁ antihistamine concentrations in plasma
c. H₁ antihistamine concentrations in tissue
d. All of above
The Receptor Occupancy Concept
Receptor Occupancy

• Antihistamine do not displace histamine once it is bound

• Having antihistamine on the receptor before histamine arrives offers best result.

• Prescription around the clock
Histamine Release during an Allergic Reaction

Receptor occupancy

= percentage of receptors occupied by a drug
10% Receptor Occupancy
60% Receptor Occupancy
Antihistamine

• $H_1$ antihistamine
  - 1$^{\text{st}}$ generation
  - 2$^{\text{nd}}$ generation
• $H_2$ antihistamine
1\textsuperscript{st} generation H\textsubscript{1}-antihistamine

- Antihistamine
- Other properties
Adverse effects of 1\textsuperscript{st} generation H1-antihistamine

Multiple aromatic (heterocyclic ring) and alkyl substituents enhance lipophilicity $\rightarrow$ penetrates blood brain barrier
**Oral $H_1$-antihistamines**

**First generation**
- short acting
- more sedation
- anticholinergic SE

**Second generation**
- long acting
- less sedation
- less side effects

- hydroxyzine, chlorpheniramine, diphenhydramine, cyproheptadine
- ceterizine, loratadine, fexofenadine, levoceterizine, desloratadine
EAACI/GA2LEN/EDF/WAO guideline: management of CU: the 2013 revision and update

Second-generation $H_1$-Antihistamine (sgAH)

If symptoms persist after 2 weeks

Increase sgAH dose (up to 4x)

$\pm H2$-Antihistamine

If symptoms persist after 1-4 weeks

Add Omalizumab, Cyclosporine A, or Leukotrieneantagonist

Short course systemic corticosteroid may be tried for exacerbations

Urticarias are very common
Acute Urticaria (<6 wks)
• History is the key
• Non-sedating antihistamine
Inducible Urticaria
• History and provocative challenges
• Non-sedating antihistamine
Chronic Urticaria
• Ethiology rarely determined
• Therapy is difficult