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Urticaria - Concurrent Breakout Session Repeated

Friday, 10 June 2011	Start 2:00pm	Duration: 60mins	Van Gogh
	Start 4:00pm	Duration: 60mins	Van Gogh

Update on urticaria

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GLORIA Global Resources in Allergy™

Adapted for New Zealand from GLORIA Module 12: Urticaria

an educational program of

WAO™
WORLD ALLERGY ORGANIZATION

Following this presentation you should be able to:

- Distinguish the various forms of physical urticaria
- Formulate a differential diagnosis and treatment plan for acute urticaria
- Describe the role of autoimmunity as a pathogenic mechanism for chronic urticaria
- Describe a therapeutic approach for patients with severe chronic idiopathic urticaria.
- Distinguish urticarial vasculitis from other forms of chronic urticaria

Description of urticaria:

- Urticaria affects up to 20-30% of the population at some time in their lifetime
- Transitory (individual episodes < 24h duration) red skin swellings with itching
- No desquamation, rarely affects mucous membranes
- Associated with angioedema in about 40% of cases

Pathogenesis of urticaria:

- Most types of urticaria are due to activation of dermal mast cells, although basophils may also be involved
- Release of histamine and other mediators (including eicosanoids, proteases, cytokines) causes local vasodilation, vasopermeability, fibrin deposition, perivascular infiltration by lymphocytes, neutrophils, and eosinophils, and pruritus
- There is minimal endothelial swelling and no leukocytoclasis

Mediators in urticaria:

- Histamine
- Leukotrienes C and D
- Platelet activating factor (PAF)
- Bradykinin
- Substance P

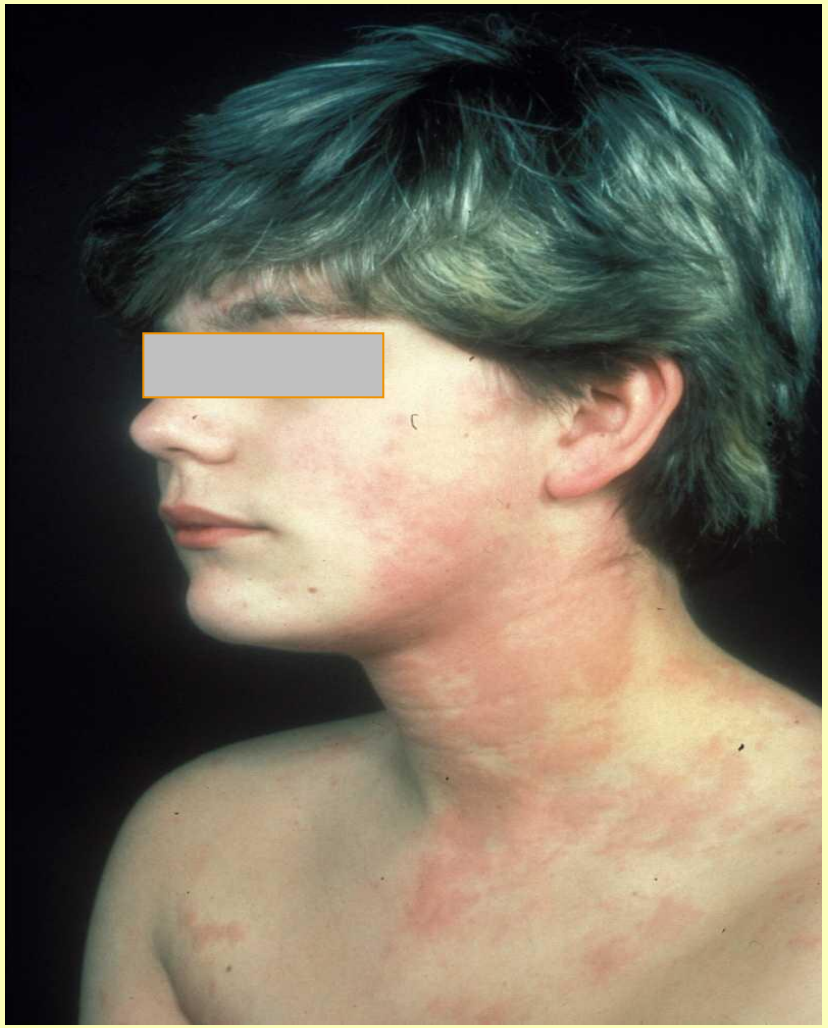
Differential diagnosis of urticaria:

- Maculopapular exanthems (viral, drug rashes)
- Eczema
- Erythema multiforme- can have an urticarial component
- Insect bite reactions (“papular urticaria”)
- Leukocytoclastic vasculitis (including urticarial vasculitis)
- Polymorphic light eruption
- Some autoinflammatory syndromes (e.g., Muckle-Wells)

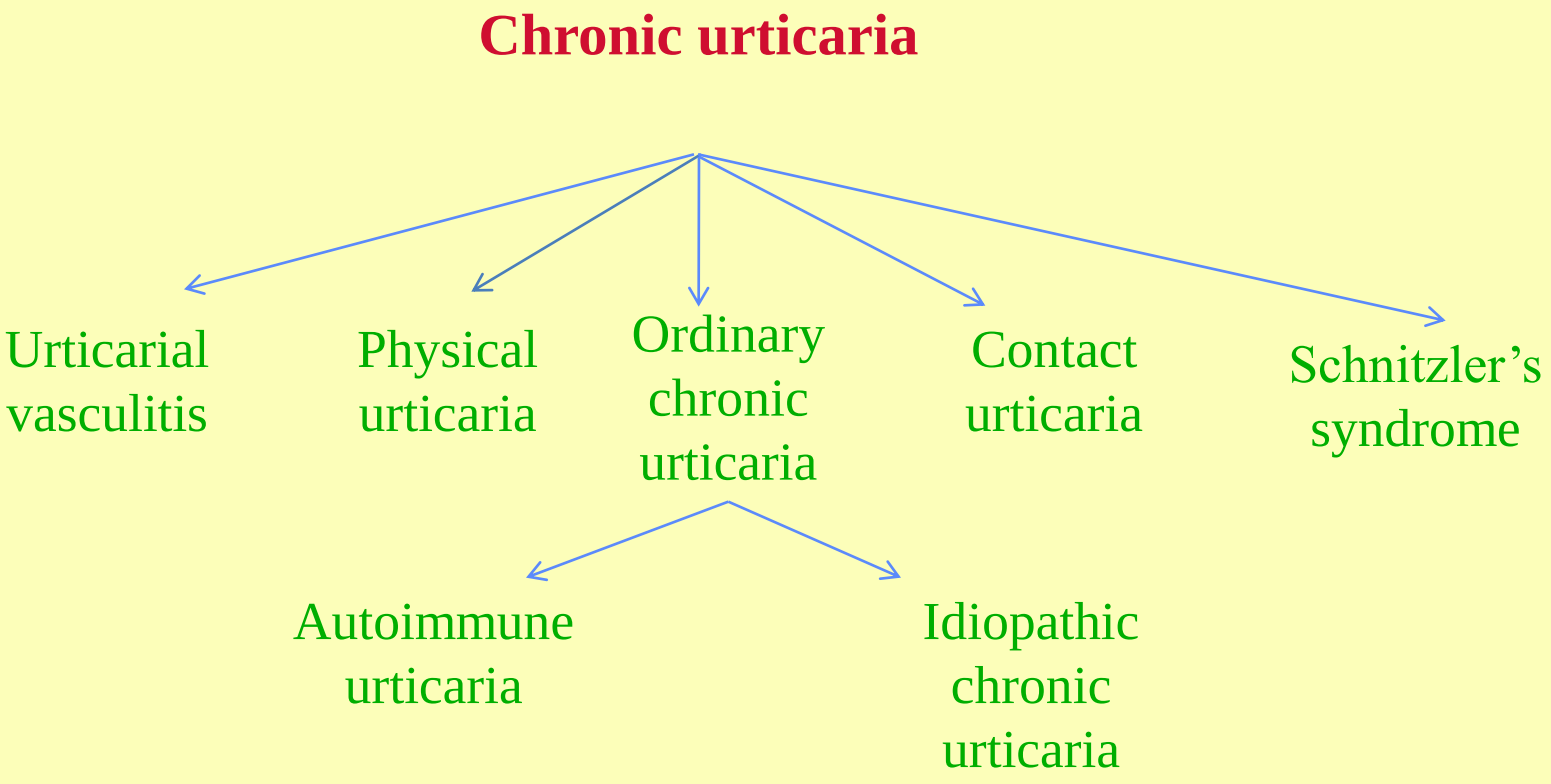
Acute vs chronic urticaria:

- "**Urticaria**" is an umbrella term inclusive of diverse clinical entities
- **Conventionally** (eg European guidelines: *Allergy*, *2004*) it is broadly divided into acute and chronic
- **Chronic urticaria** is conventionally defined as "daily or almost daily urticarial eruptions occurring for 6 weeks or more"
- **Chronic urticaria** is further subclassified into several distinct entities

Urticaria:



Classification of chronic urticaria:



Acute urticaria:

- All ages; common in childhood
- Pruritus less intense in children
- Abrupt onset of urticarial eruption usually pruritic and widespread
- Angioedema common
- Systemic symptoms (fever, malaise) uncommon, depending on cause
- Duration: usually hours or days

Triggers for acute urticaria:

- **Viral infections**; particularly in children. In adults: prodrome of Hepatitis B, infectious mononucleosis (EBV)
- **Drugs** (NSAIDS, penicillins and derivatives, radiocontrast media)
- **Foods** non–allergic (e.g., scombroid fish poisoning) and allergic (IgE–mediated) (e.g., nuts, shellfish)
- **Immunization vaccines** e.g., MMR, tetanus toxoid
- **Insect bites or stings**
- **Allergy to latex**
- C**ontact urticaria**

Investigation of acute urticaria:

- **Many cases require no investigation -** the cause may be obvious to patient and doctor alike
- **Skin prick tests** may support the diagnosis (but avoid SPT in severely affected patients, and in patients with current angioedema or a history of angioedema). May not be possible while on antihistamines
- **Serum IgE testing** may also help confirm the culprit- can be done while on antihistamines

Management of acute urticaria:

- Many attacks of acute urticaria are solitary, and the cause is evident and avoidable
- Facial / labial / buccal angioedema should respond to antihistamines and or prednisone
- Severe oropharyngeal angioedema should prompt overnight admission. Adrenaline may be required
- Phenergan by injection- avoid IV administration of phenergan because of hypotension. IM/IV hydrocortisone can be given.
- Prednisone may be needed acutely

Food allergy as a trigger for acute urticaria:

- Mediated by binding of allergens that survive digestion, and delivered to the skin to interact with IgE on cutaneous mast cells
- Can be diagnosed by skin test or RAST assay – result must be correlated with history and be reproducible
- Double-blind oral challenge represents the definitive test for diagnosis
- See accompanying talk

Drug hypersensitivity as a trigger for acute urticaria:

- Drug or drug metabolite causing hives by interaction with IgE antibody on cutaneous mast cells ***Example: Penicillin allergy***
- Non-IgE mediated reactions that depend on drug metabolism with resultant mast cell activation or direct interaction with small venules ***Example: NSAID reactions***
- Direct mast cell degranulation by drugs ***Example: Opiates***
- Osmotic cell degranulation and alternative complement pathway activation ***Example: Radiocontrast reactions***

Physical urticarias:

Common:

- Symptomatic dermographism (also called factitious urticaria)
- Delayed pressure urticaria
- Cholinergic urticaria

Less common:

- Cold contact urticaria

Rare:

- Solar urticaria
- Heat contact urticaria
- Aquagenic urticaria
- Vibratory angioedema

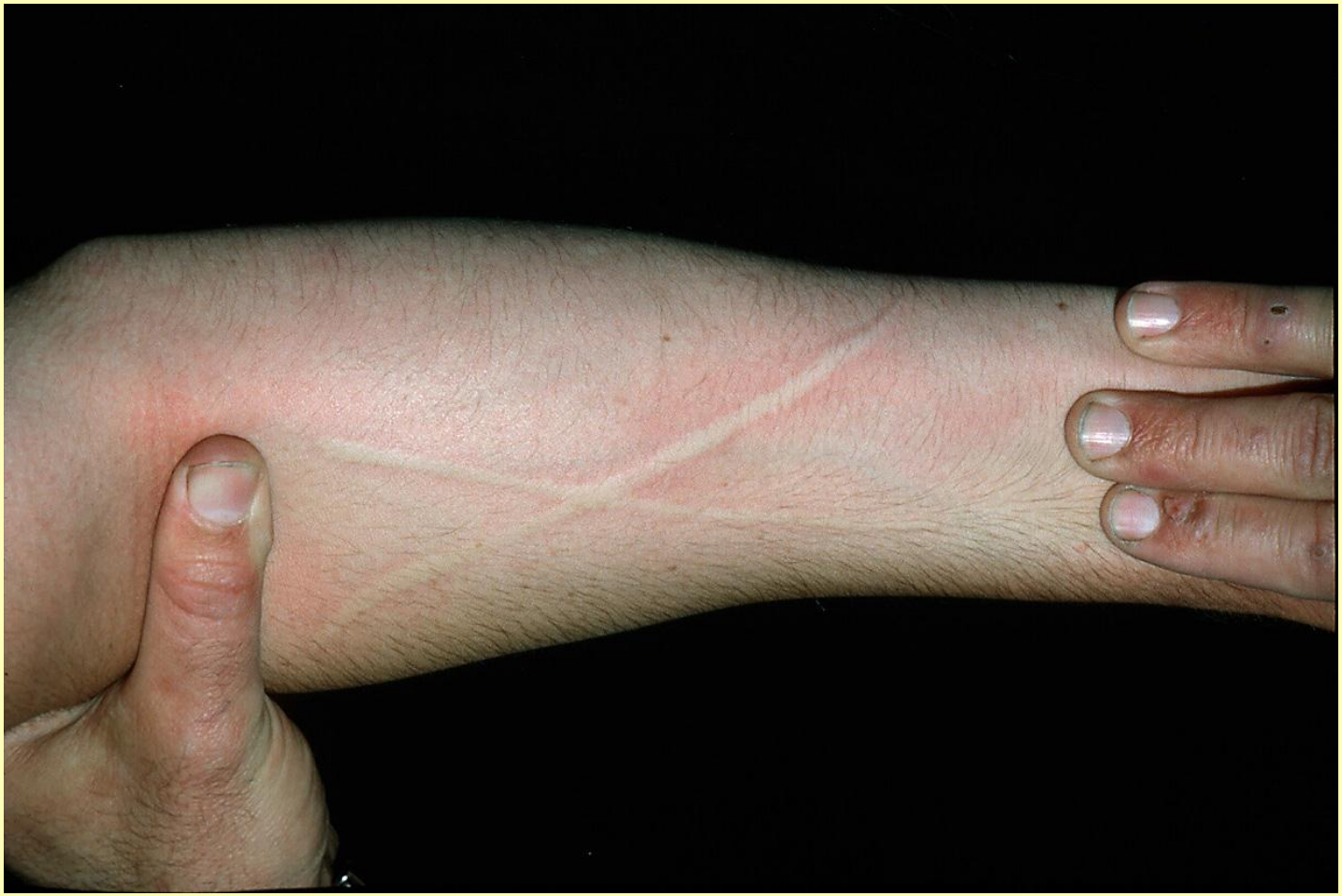
Physical urticarias:

- Hives last less than 2 hours
- Stimulus (e.g., ice cube test, exercise, scratching) has no late phase response
- Treated readily with antihistamines but may require high doses
- Do not respond to corticosteroids

Dermatographia:

- Common physical urticaria, frequently overlooked
- Generalized pruritus and red wheals, aggravated by scratching, rubbing, tight or coarse clothing
- Mucous membranes usually unaffected, no angioedema
- Can be intense

Dermatographia:



Dermatographia:

- Patients complain of itch (even if hives not present), skin “crawling” and worsening hives with scratching
- Particularly prominent over pressure points where clothing is tight or rubbing
- Can be associated with lip swelling without other evidence of angioedema
- When severe, may be confused with other types of chronic urticaria

Treatment of dermatographia:

- Non-sedating antihistamines; loratadine, fexofendadine, cetirizine, desloratidine, levocetirizine
- May combine agents for more severe cases, e.g., fexofenadine in the morning, Phenergan at bedtime
- For unresponsive cases to the above:

  add Doxepin at night.- risk of sedation the next day

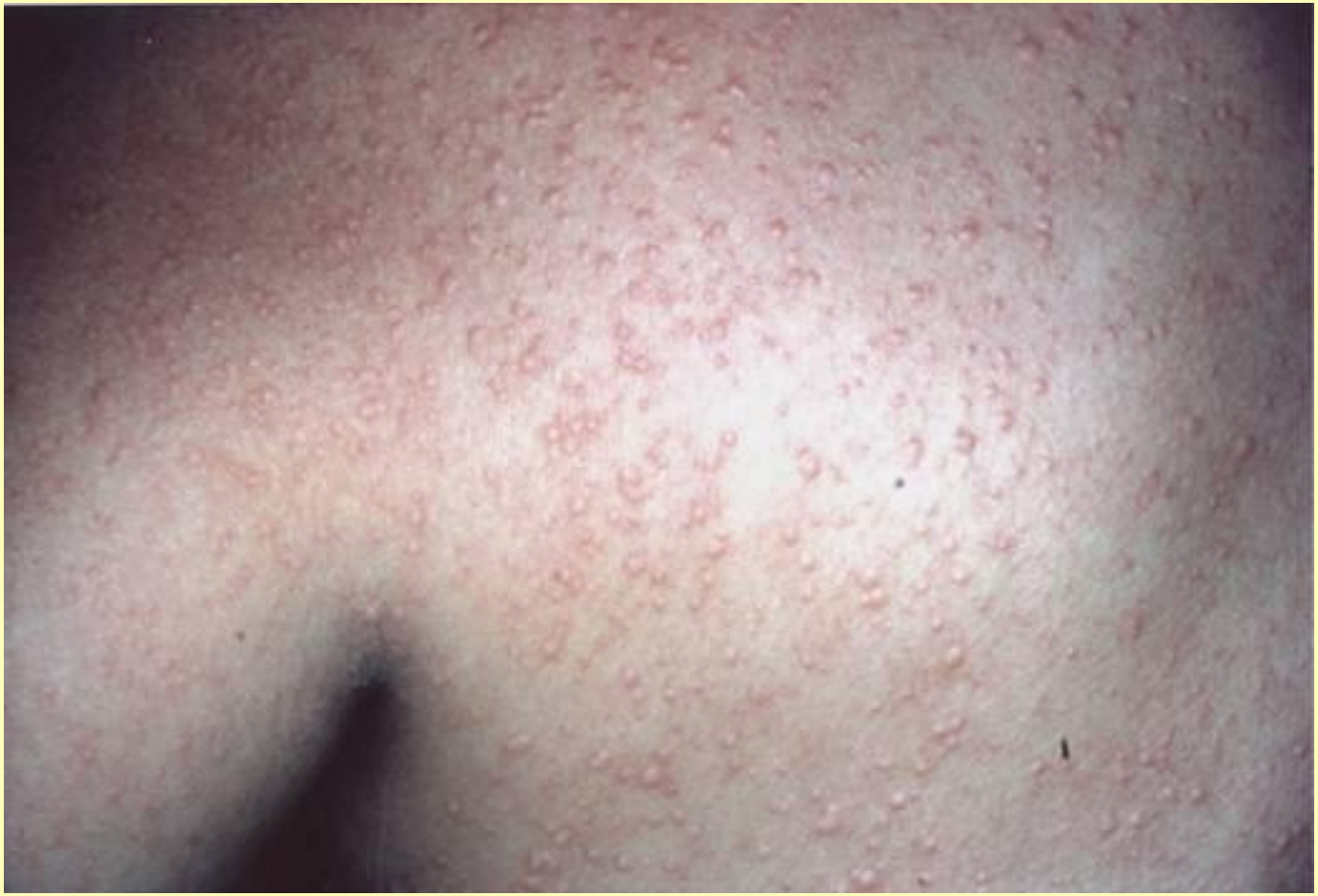
Cholinergic urticaria

- Very common in older children, young adults
- Transitory pruritic symmetrical red maculopapular rash on neck trunk, limbs after exercise, heat, emotion
- Occasionally associated bronchospasm in more severe cases, rarely angioedema

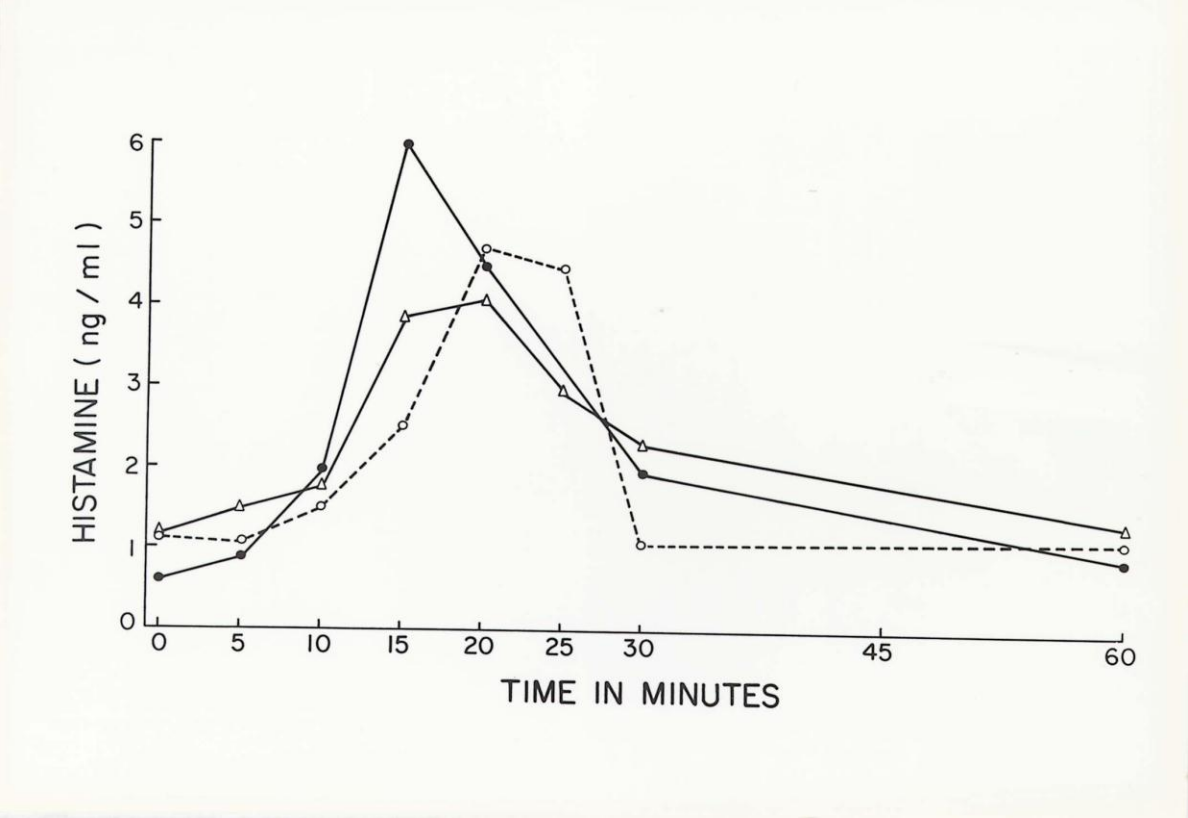
Cholinergic urticaria

- Hives begin on neck, trunk, and spread to face and extremities
- Triggered by exercise, sweating, hot showers, strong emotion; Exercise induction is reproducible; requires increase in core body temperature
- Small punctate urticarial lesions a few mm in diameter with prominent erythema
- Histamine release demonstrated within circulation after exercise challenge

Cholinergic urticaria



Cholinergic urticaria: histamine release during exercise



Cholinergic urticaria

- **Diagnosis**: exercise challenge eg treadmill or jogging in place usually elicits a positive response. Heat challenge e.g., hot bath to evoke the rash
- **Investigation**: none indicated
- **Treatment**: usually responds to H1 antihistamines, anabolic steroids eg, danazol effective in severely affected cases- specialist procedure
- **Prognosis:** usually resolves in months / a year or two

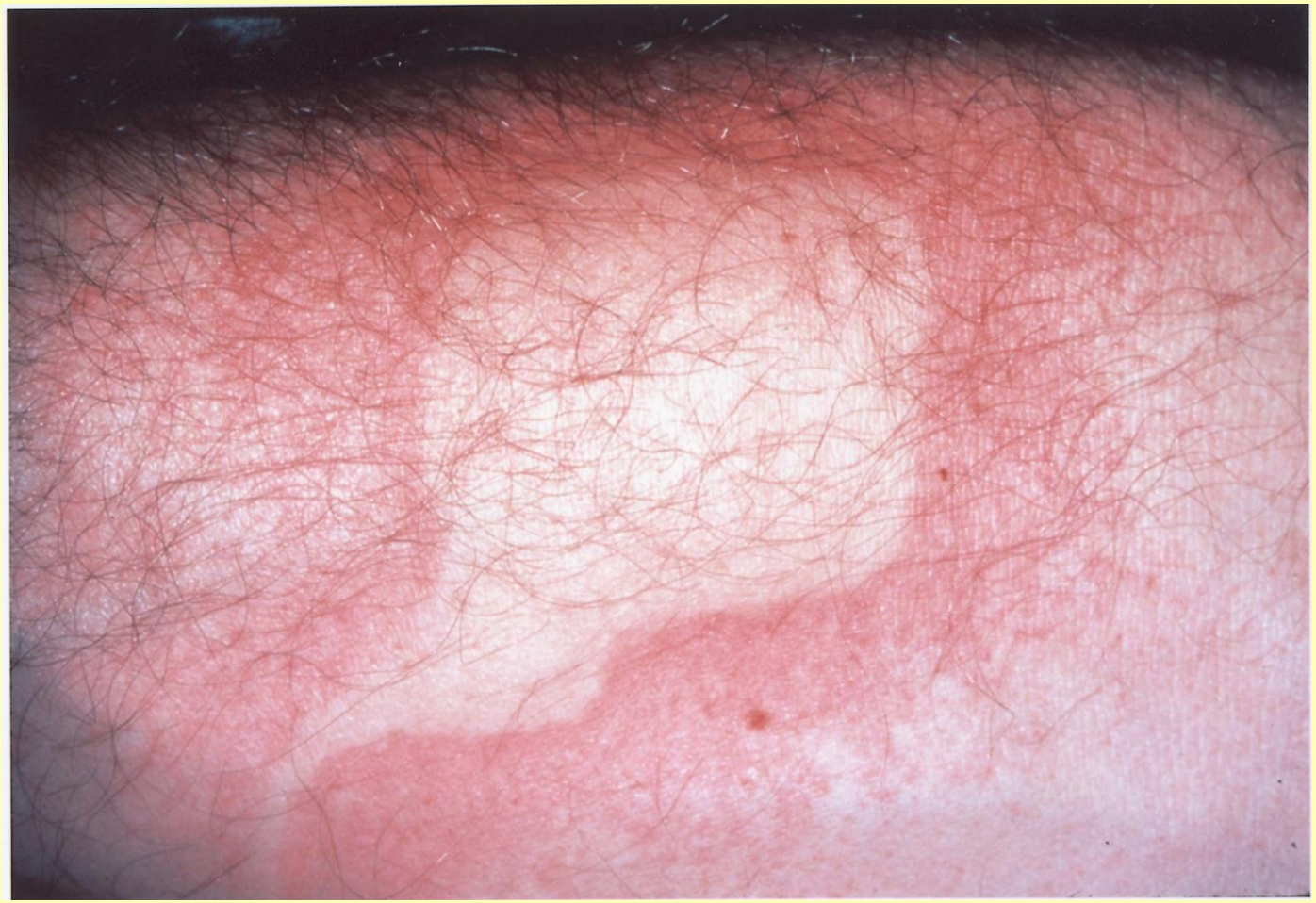
Cold urticaria:

- Redness, whealing itching on skin exposed to cold surfaces, water, air
- Angioedema can occur locally e.g., lips, tongue after sucking an iced-popsicle
- If generalized (e.g., swimming), can be life threatening (syncope)

Cold urticaria:

- **Diagnosis:** place icepack on uninvolved skin for 5 min, remove and inspect site for cold–evoked wheal 5 min after removal
- **Investigations**: cryoglobulins and cold agglutinins commonly sought but rarely found
- **Treatment:** usually responds to avoidance + H1 antihistamines. Cold tolerance treatment ("cold desensitization") is effective in selected cases
- **Severity** depends on temperature threshold for reacting

Cold urticaria:



Other physical urticarias:

Solar urticaria:

- **Diagnosis:** expose skin to direct sunlight, slide projector lamp; a local pruritic wheal and flare reaction denotes a positive result
- **Treatment**: avoidance, H1 antihistamines, light tolerance treatment in selected patients

Heat contact urticaria:

- **Diagnosis:** place warm beaker base (45^{o} C) on clinically uninvolved skin for 5 min; a local pruritic wheal and flare reaction denotes a positive result
- **Treatment:** avoidance and H1 antihistamine

Other physical urticarias:

Aquagenic urticaria:
Diagnosis: expose face, neck upper trunk skin to tepid water (eg squeezing a sponge); elicits a transitory pruritic erythematous maculopapular eruption

Vibratory angioedema:
Diagnosis: vibrate forearm with a laboratory vortex or rub a towel vigorously across the back (assuming no dermatographism).

Treatment: avoidance and H1 antihistamines

Other physical urticarias:

1) **Chronic urticaria**:
    a) Idiopathic
    b) Autoimmune

2) **Cutaneous vasculitis**:
    a) Idiopathic
    b) Connective tissue diseases
    c) Hypocomplementemic urticarial vasculitis syndrome

3) **Genetic autoinflammatory syndromes**

4) **Miscellaneous, e.g., Schnitzler's Syndrome**

Aggravating factors for chronic urticaria:

- Non-steroidal anti-inflammatory drugs (NSAIDS)
- Certain “pseudoallergens” in foods (controversial)
- Consumption of alcohol
- Intercurrent viral infections
- Stress / overtiredness

Associations of chronic urticaria

- **Angioedema:** occurs in 40-80% of patients in different series, mainly affecting the eyelids, lips or tongue. Although alarming it is never fatal
- **Physical urticarias:** (usually symptomatic dermatographism, or delayed pressure urticaria) occur in about 50%
- **Functional thyroid disease:** (hypo- or hyperthyroidism) occurs in about 20% and Hashimoto's disease is found in about 15%

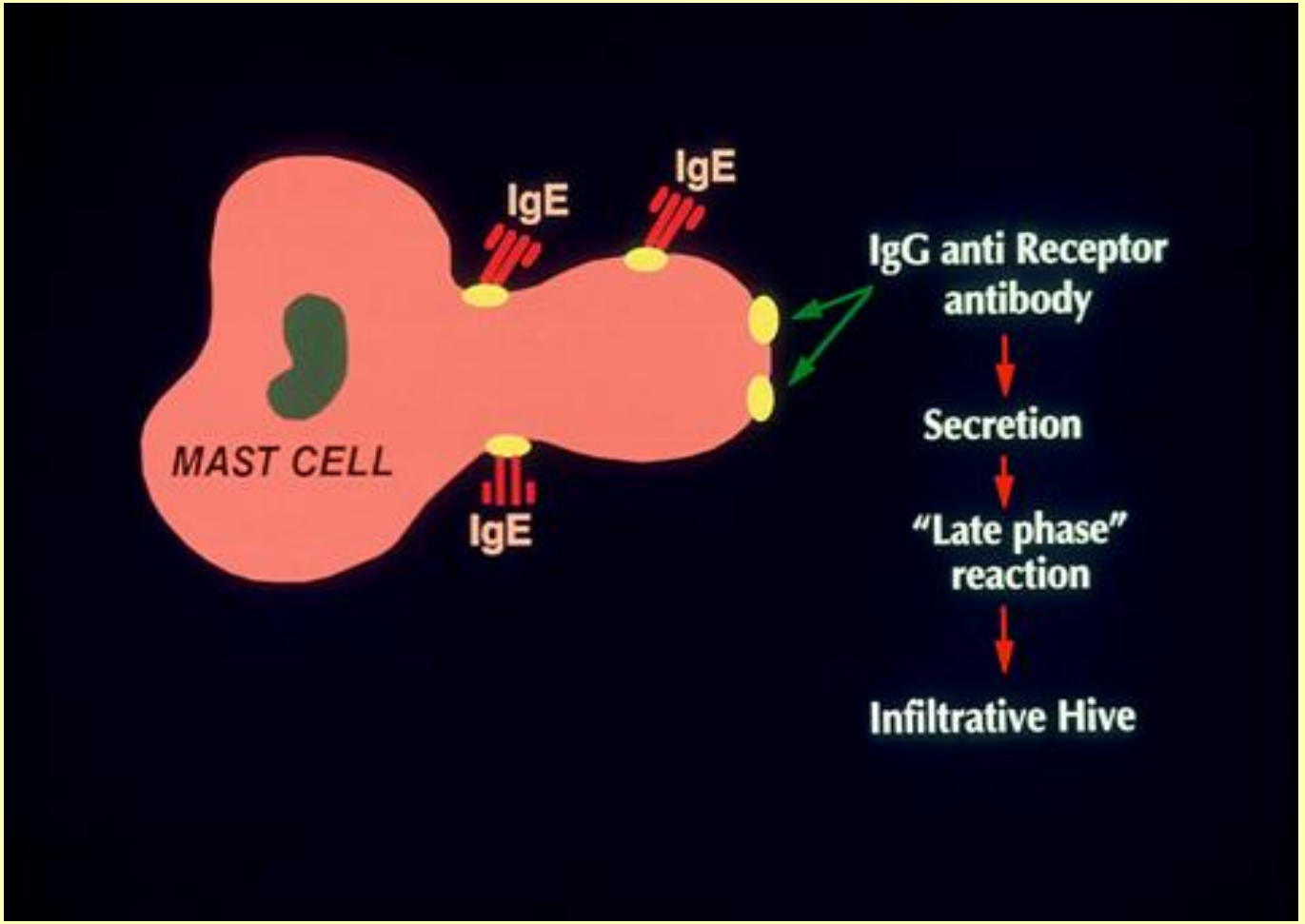
Other physical urticarias:

Patients with chronic urticaria are almost invariably over-investigated

Necessary investigations include:

- FBC, differential WBC, ESR, CRP
- Thyroid function and thyroid autoantibodies screen
- In-patients with a poor response to antihistamines, a skin biopsy should be performed to exclude urticarial vasculitis

Autoimmune chronic urticaria:



Autoimmune chronic urticaria:

1. IgG antibody to IgE receptor cross-links adjacent α subunits to cause cutaneous mast cell (and basophil) activation

2. Predominant IgG antibody subclasses are IgG_1 and IgG_3 which are complement fixing

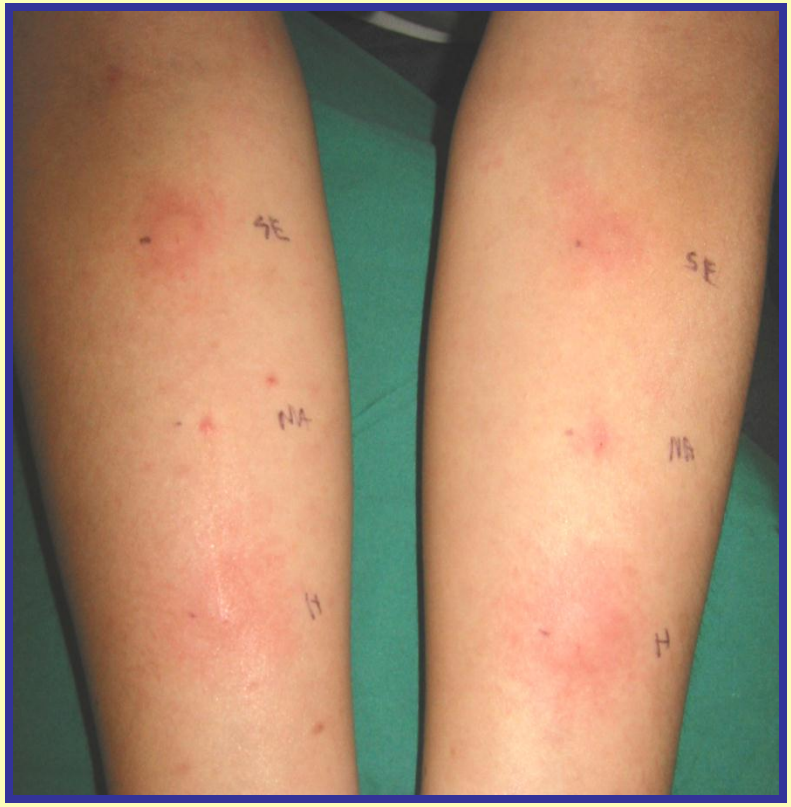
3. Complement activation by two adjacent IgG-F_c regions (requires 4 IgE receptor α subunits)

4. Release of C5a anaphylatoxin from C5 which augments histamine release

Pathology of chronic urticarias:

1. Non-necrotizing perivascular infiltration
2. Integrity of vessel wall maintained
3. Predomination of CD4(+) lymphocytes with mixture of TH1 and TH2 cells. No basophils. Few CD8(+) cells
4. Variable number of neutrophils and eosinophils – more prominent in chronic autoimmune urticaria than chronic idiopathic urticaria

Serum autologous intradermal sking test



Chronic urticaria: general advice

- Avoidance of:
- NSAIDS, alcohol, spicy foods
- Overtiredness and stress
- Wearing of tightly fitting garments, footwear
- Strenuous physical exercise
- Overheated ambient temperature

Drugs for chronic urticaria

- H_1 receptor antagonists
- H_2 receptor antagonists
- Leukotriene antagonists
- Alternate-day corticosteroids
- Cyclosporin- rarely used many adverse effects

Second line drugs for refractory chronic urticaria

- **Add montelukast 10mg daily:** It helps some but not all patients and adverse effects are rarely a problem
- **Add doxepin 25mg at night:** This tricyclic is best known as an anti-depressant, but is a very potent H1 and H2 antihistamine, causing sedation. It should not be given with other antidepressants
- **Prednisolone:** short tapering courses commencing 30mg daily are useful to deal with the occasional temporary flare-up

Third line rugs for chronic urticaria

- Additionally, intravenous immunoglobulin and plasmapheresis have proved highly effective in some selected refractory cases
- There are now emerging reports of the effectiveness of the anti-IgE monoclonal omalizumab in both autoimmne and non-autoimmune chronic urticaria- currently being trialled

Urticarial vasculitis

- Individual wheals persist for more than 24h, and may leave residual staining
- Itching is inconsistent, and wheals may be tender and painful
- In a minority hypocomplementaemia is present associated with systemic symptoms including arthralgia
- Response to antihistamine treatment is poor
- Morphology of urticarial eruption is often indistinguishable from chronic ordinary urticaria

Causes of urticarial vasculitis

- **Autoimmune connective tissue disease:** (Sjogren's syndrome, systemic lupus, rheumatoid arthritis)
- **Viral hepatitis:** (hepatitis B, C)
- **Paraproteinaemia:** (Schnitzler's syndrome occasionally has a vasculitic histology)
- **Inflammatory bowel disease**

Diagnostic work up for urticarial vasculitis

- Complement screen
- ESR, CRP
- Viral screen (hepatitis B, C)
- Plasma protein electrophoretic analysis
- ANA, rheumatoid factor, anti-Ro
- Chest X ray, ECG, Echocardiogram

Treatment of urticarial vasculitis

- Antihistamines are usually ineffective; the following may be effective:
- Dapsone (screen for G6-PD deficiency)
- Colchicine
- Hydroxychloroquine
- Prednisolone (especially in patients with systemic involvement)
- Intravenous immunoglobulin
- Plasmapheresis

Contact urticaria

- Eliciting substance causes local wheal and flare within minutes of application to skin
- May be associated with systemic symptoms: rhinitis, conjunctivitis, bronchospasm, angioedema, anaphylaxis
- Classified as immunological, non-immunological
- Due to release of histamine and eicosanoids, especially prostaglandin D2 from dermal mast cells

Triggers for contact urticaria

Immunological:

- House dust mite
- Dairy products
- Fruits
- Nuts, especially peanuts
- Meats
- Sea foods
- Vegetables, esp. garlic, onion
- Fragrances
- Hair care products
- Medications, esp. antibiotics
- Plant products, esp. latex

Non-immunological:

- Foods, especially fish
- Fragrances, flavorings
- Medicaments
- Animals, esp. caterpillars, jellyfish
- Plants, esp. nettles, corals
- Preservatives, antiseptics
- Ammonium persulphate

Management of contact urticaria

- Treatment consists of identification of culprit, avoidance and patient education
- Severe reactors (eg peanut contact urticaria) should wear an inscribed bracelet listing the culprit plus cross reacting substances, and should carry antihistamines and self administration adrenaline (epinephrine)

Summary: treatment depends on duration of symptoms Acute vs chronic urticaria:

- "**Urticaria**" is an umbrella term inclusive of diverse clinical entities
- **Conventionally** (eg European guidelines: *Allergy*, *2004*) it is broadly divided into acute and chronic
- **Chronic urticaria** is conventionally defined as "daily or almost daily urticarial eruptions occurring for 6 weeks or more"
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