Update on urticaria
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Adapted for New Zealand from GLORIA Module 12: Urticaria
an educational program of

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
• Be aware of which patients should be referred

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 (e.g., 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.

**Classification of chronic urticaria:**

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Chronic urticaria
  └── Urticarial vasculitis
      └── Physical urticaria
          └── Ordinary chronic urticaria
              └── Contact urticaria
                  └── Schnitzler’s syndrome
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**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**
- **Contact 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
- **Specific 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 sIgE assay – result must be correlated with history and be reproducible
- Double-blind oral challenge represents the definitive test for diagnosis
- See accompanying talk on FA

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 with antihistamines but may require high doses. Antihistamines may not be effective.
- 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
- Does not always respond to antihistamines.
**Treatment of dermatographia:**

- Non-sedating antihistamines: loratadine, fexofenadine, cetirizine, desloratadine, 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

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**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

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**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

- **Diagnosis:** Exercise challenge e.g., 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 e.g., danazol effective in severely affected cases—specialist procedure. Refer if no response to treatment.
- **Prognosis:** Usually resolves in months/a year or two.

### Cold Urticaria

- **Diagnosis:** Place ice pack on uninvolved skin for 5 min, remove and inspect site for cold-evoked wheal 5 min after removal.
- **Investigation:** 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.
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 ($45^\circ C$) on clinically uninvolved skin for 5 min; a local pruritic wheal and flare reaction denotes a positive result
- **Treatment:** avoidance and H1 antihistamine

**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

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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
  - Tryptase
  - In patients with a poor response to antihistamines, a skin biopsy should be performed to exclude urticarial vasculitis
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 IgG₁ and IgG₃ which are complement fixing
3. Complement activation by two adjacent IgG-Fc 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. Predominance 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

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

- H₁ receptor antagonists
- H₂ 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. Beware of depression risk and emotional lability
- **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 literature of the effectiveness of the anti-IgE monoclonal omalizumab in both autoimmune and non-autoimmune chronic urticaria - currently being trialled. Not funded in NZ.
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
- Needs skin biopsy
Treatment of urticarial vasculitis

- Antihistamines are usually ineffective; the following may be effective:
  - Treat underlying cause eg SLE
  - Dapsone (screen for G6-PD deficiency)
  - Colehicine
  - 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

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<tr>
<th>Immunological</th>
<th>Non-immunological</th>
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<tbody>
<tr>
<td>House dust mite</td>
<td>Foods, especially fish</td>
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<tr>
<td>Dairy products</td>
<td>Fragrances, flavorings</td>
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<tr>
<td>Fruits</td>
<td>Medicaments</td>
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<tr>
<td>Nuts, especially peanuts</td>
<td>Animals, esp. caterpillars, jellyfish</td>
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<tr>
<td>Meat</td>
<td>Plants, esp. nettles, corals</td>
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<tr>
<td>Sea foods</td>
<td>Preservatives, antisepsics</td>
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<tr>
<td>Vegetables, esp. garlic, onion</td>
<td>Ammonium persulphate</td>
</tr>
<tr>
<td>Fragrances</td>
<td>Medications</td>
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<tr>
<td>Hair care products</td>
<td>Antiseptics</td>
</tr>
<tr>
<td>Medications, esp. antibiotics</td>
<td>Antiseptics</td>
</tr>
<tr>
<td>Plant products, esp. latex</td>
<td>Antiseptics</td>
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Management of contact urticaria

• Treatment consists of identification of culprit, avoidance and patient education

• Severe reactors (e.g., 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

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Summary: specialist referral

• Acute urticaria- not settling or where cause is not clear

• Chronic urticarias, not responding to treatment

• Other urticarias e.g., suspected vasculitis