An approach to chronic Urticaria

Dr Claudia Gray
MBChB, MRCPCH, MSc, DipAllergy, DipPaedNutr
Paediatric Allergist, Red Cross Children’s Hospital and Vincent Pallotti Hospital, Cape Town
claudiagray.paediatrics@gmail.com
Introduction

- Chronic urticaria ± angioedema are not life threatening, but
- Cause misery, embarrassment, discomfort
- ↓ QoL comparable to triple coronary heart disease

Introduction

- There is no cure
- Adequate treatment should enable patient to lead an essentially normal life
- Patients are entitled to expect effective treatment to achieve this goal, which in selected cases may involve potent and expensive medications
Introduction: definitions

- **Chronic urticaria (CU)** is a condition in which wheals, with or without concomitant angioedema, occur daily or near daily for \( \geq 6 \) weeks.
- Includes episodic acute intermittent urticaria/angioedema lasting hours-days and recurring over months or years.
- Prevalence approx 1% of population.
Introduction: definitions

- **Acute urticaria (CU)** is a single episode of urticarial illness lasting < 6 weeks
- Prevalence approx 15% of population
- Usually self-limiting
- Cause more likely to be found
Introduction: definitions

• Angioedema without urticaria requires a different approach
• Rule out hereditary angioedema (HAE) - which behaves differently to CU and can be life threatening
What is Urticaria?

- Hives/wheals/weals/welts/”bommels”
- Red raised itchy rash or pale with surrounding flare
- Superficial skin layers
- Mast cell activation → release of histamine and other inflammatory mediators →
- Increased blood flow and vascular permeability in superficial skin layers
What is Urticaria?
What is Urticaria?

- Lesions single or numerous
- Few mm to hand-sized
- Arise spontaneously, peak between 8-12 hours, resolve by 24 hours.
- Extremely itchy; characteristically relieved by rubbing as opposed to scratching
What is Urticaria?
What is Angioedema?

- Tissue swelling as a result of ↑ vascular permeability in the deeper layer of the skin (dermal/subcutaneous)
- Most evident in the oropharynx, around eyes, abdomen and genitalia
- Involves mucous membranes, unlike urticaria
What is Angioedema?
What is Angioedema?
What is Angioedema?

- Angioedema is painful rather than itchy
- Can persist for several days
- Life threatening airway compromise has not been described with chronic urticaria with angioedema (unlike HAE)
Co-existence of Urticaria and Angioedema?

- Urticaria alone in 20-50% cases CU
- Urticaria + angioedema in 40-80%
- Angioedema alone in 10%
Mechanisms

Trigger

↑ mast cell releasibility

• Immediate release of histamine

• Subsequent release of membrane derived mediators (leukotrienes, PG)
  • Other non-histamine mechanisms eg C5a

• Perpetuation of inflammatory response by cellular infiltrate
Mechanisms

- Release of mediators is confined to the skin and submucosa, thus the cardiorespiratory compromise of anaphylaxis does not occur.
Mechanisms

- What causes mast cell activation?
- In many cases unknown (idiopathic)
- In some cases IgE receptor is chronically stimulated by IgG antibodies (autoimmune)
- Other triggers
Aetiology

- What causes persistent/recurrent mast cell activation in CU?

- Causative versus aggravating factors
- FACT: majority of patients with CU are referred to allergy clinics to determine what food/preservative they are allergic to
- REALITY: majority are “idiopathic” and hopelessly over-investigated
Aetiology

• **FACT:** majority of patients with CU are referred to allergy clinics to determine what food/preservative they are allergic to

• **REALITY:** majority are “idiopathic” and hopelessly over-investigated
### Aetiological Classification of CU

<table>
<thead>
<tr>
<th>AETIOLOGY</th>
<th>COMMENTS</th>
</tr>
</thead>
<tbody>
<tr>
<td>IDIOPATHIC</td>
<td>40-50% of cases</td>
</tr>
<tr>
<td>AUTOIMMUNE</td>
<td>Autoantibodies to IgE/IgE receptor: 30-50%</td>
</tr>
<tr>
<td>PHYSICAL STIMULI</td>
<td>Cold, aquagenic, cholinergic, pressure</td>
</tr>
<tr>
<td>DRUG INDUCED</td>
<td>ACEI, NSAIDS</td>
</tr>
<tr>
<td>ALLERGIC CONTACT</td>
<td>Contact urticaria to latex/food/grass</td>
</tr>
<tr>
<td>NON-IgE MEDIATED MAST CELL DEGRANULATION</td>
<td>E.g. opiates</td>
</tr>
<tr>
<td>CI INHIBITOR DEFICIENCY</td>
<td>Angioedema without urticaria</td>
</tr>
<tr>
<td>FOOD CONSTITUENT</td>
<td>Rare! But often perceived as the cause</td>
</tr>
<tr>
<td>LYMPHOProliferative Disorders</td>
<td></td>
</tr>
<tr>
<td>VASCULITIS</td>
<td>Painful urticaria</td>
</tr>
<tr>
<td>CRYOPYRIN ASSOCIATED PERIODIC SYNDROME; SCHNITZLER’S SYNDROME</td>
<td>Extremely rare, cold associated systemic symptoms</td>
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</table>
Aetiological Classification

- idiopathic
- autoimmune
- others
1. Chronic Idiopathic Urticaria

- Majority of CU cases
- No consistent relationship with aetiological agent
- Triggering stimulus is elusive
- Unpredictable mast cell granulation
- Investigations typically negative, and should be minimal
Chronic Idiopathic Urticaria

- May be aggravated by:

1. **Viral infections**:  
   - Worsened for up to 6 weeks afterwards

2. **Stress**:  
   - Possibly via ↑ release of corticotrophin-releasing hormone (CRH) in the skin  
   - Attach to CRH-receptor on mast cells which trigger degranulation
2. Autoimmune Chronic Urticaria

- Subgroup of CIU which test positive to autoantibodies:
  - Most commonly IgG antibody to α-subunit of IgE receptor on mast cells
  - Rarely IgG to IgE which is bound to mast cells
- 30-50% of adults and children with chronic urticaria
- Mast cells chronically stimulated
Autoimmune Chronic Urticaria

- Pathogenesis also involves activation of classical complement pathway and stimulation of complement C5a

- Explains why autoimmune activation is confined to the skin as the lung does not have C5a receptors
Autoimmune Chronic Urticaria

- 30-50% of adults and children with CU have positive autoimmune tests

- Associated in 30% of adults with antithyroid antibodies, indicating a general autoimmune tendency
Autoimmune Chronic Urticaria

- **Diagnostic tests:**
  1. **Autologous serum skin test**
     - 0.1 mL of patient’s serum is injected into patients forearm intradermally, with a saline control. Watch for swelling and flare after 25-30 minutes
     - 70-80% sensitive and specific
  2. **Measurement of levels of the anti-IgE antibodies**
     - Only in specialised overseas laboratories
Autologous serum skin test
Autoimmune Chronic Urticaria

- Importance of making a diagnosis:
  - Provides an explanation
  - Prognostication: usually a more intense, difficult to treat and protracted course
  - Makes further investigations unnecessary
3. Food Triggers

- Very very rarely the cause
- Patients frequently analyse foods/additives they have eaten that day in search of a connection with symptoms
**Food Triggers**

<table>
<thead>
<tr>
<th>Genuine IgE mediated Food Allergy</th>
<th>“Food reaction” in CU</th>
</tr>
</thead>
<tbody>
<tr>
<td>Occur within 2 hours of ingestion</td>
<td>CU rash often starts in the night or early morning hence &gt; 6 hours after eating</td>
</tr>
<tr>
<td>Symptoms are reproducible after each exposure</td>
<td>Symptoms not reproducible with each exposure</td>
</tr>
<tr>
<td>Short lived wheals &lt; 6 hours</td>
<td>Wheals come and go over several days</td>
</tr>
<tr>
<td>Part of a complex of symptoms eg flushing, pruritis, gastrointestinal, chest or cardiovascular symptoms</td>
<td>Only wheals ± angioedema</td>
</tr>
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</table>
Food Triggers

- Preservatives/Additives?
- Not the cause; may be a trigger/aggravator
- Cohort at RXH, 10% of CU sufferers were sensitised to preservatives (NB benzoates, tartrazine); elimination caused some ↓ frequency of symptoms but did not “take it away”
- CAST tests to preservatives are available
- Salicylates may trigger CU by a non-IgE mediated mechanism
Food Triggers

- Patients with CU may report worsening with rich fermented/spicy food or alcohol

- Probably related to histamine content and vasodilatory properties of these foods rather than an allergy
Allergic Contact Urticaria

- Local urticaria after contact with allergens via an IgE-mediated mechanism

- Eg latex, egg, dog saliva, grass

- Diagnosed by SPT and specific IgE levels
Infections

- Association of CU with parasites, EBV, Hep B, viral infections, fungal infections
- Very rarely causative
- Diagnostic testing directed by clinical history
- Mechanism: immune complex formation with antibody and antigen, leading to c5a activation which binds to mast cell receptors
Infections

- Helicobacter Pylori
  - was in vogue as potential cause of CU a few years ago
  - results not reproducible
  - high background of asymptomatic H pylori infection makes interpretation difficult
Physical Urticarias

- Urticaria induced reproducibly by a physical stimulus
- Physical trigger causes direct mast cell activator release
- Symptoms usually of quick onset and short duration
- Often resistant to standard therapy
- Can occur in conjunction with CIU/Autoimmune urticaria
- Diagnosed by challenge tests to appropriate stimuli
Physical Urticarias

- A. Dermatographism
Physical Urticarias

B. Cholinergic urticaria
  - Exercise, emotion
  - Pin point wheals with flare
Physical Urticarias

- C. Delayed pressure urticaria
  - Sitting, lying, tight clothes
Physical Urticarias

- D. Cold Urticaria
Physical Urticarias

- Exercise
- Solar urticaria
- Aquagenic urticaria
- Vibratory (use of vibratory building tools)
Drug Induced Urticaria

- NSAIDS
- Aspirin
- Antidepressants (citalopram)
- Statins
- Anti-epileptics
- Opiates

- Generally via a non-IgE mediated mechanism
Urticarial Vasculitis

- Small vessel vasculitis due to deposition of immunoglobulins and complement
- Assoc with infections, autoimmune disorders, malignancy
- Symptoms such as fever, weight loss, lymphadenopathy
- Lesions last > 24 hours
- Leave bruising
- Painful rather than itchy
- Skin biopsy usually needed for diagnosis
Urticarial Vasculitis
Angioedema without Wheals

3 possibilities:

- CU variant
- Hereditary angioedema
- Drug Induced (ACEI)
Angioedema without Wheals

- ACEI-related angioedema 0.1-0.2%
- Can occur several weeks or months after starting the medication
- Involves ↑ bradykinin
- Can involve larynx, hence all ACEI treatment should be withdrawn
- Swelling may take weeks to months to settle
- Angiotensin receptor blocking drugs can usually be used
## Angioedema without Wheals

- **2. C1esterase inhibitor deficiency**

<table>
<thead>
<tr>
<th>Hereditary angioedema type 1</th>
<th>Hereditary angioedema type 2</th>
<th>Acquired</th>
</tr>
</thead>
<tbody>
<tr>
<td>• Hereditary</td>
<td>• hereditary</td>
<td>• C1 inhibitor deficiency caused associated with malignancies e.g. paraproteinaemias</td>
</tr>
<tr>
<td>• Low levels of C4 and C1 inhibitor levels</td>
<td>• Normal levels but poor functioning C1 inhibitor</td>
<td></td>
</tr>
</tbody>
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Diagnosis of Chronic Urticaria

1. Clinical History
   - KEY!
   - Nature of lesions?
   - Duration?
   - Residual bruising?
   - Angioedema?
   - Other symptoms?
   - Family history angioedema/unexplained abdo pain/unexplained airways obstruction etc
   - Drug History
Diagnosis of Chronic Urticaria

2. Special Investigations

- Basic screen:

1. FBC
2. ESR
3. Urine dipstick
4. TFT and autoantibodies
Diagnosis of Chronic Urticaria

2. Special Investigations

- Basic screen:

1. FBC
   (eosinophilia/anaemia/neutrophilia)
2. ESR
   (chronic infection/vasculitis/paraproteinaemia)
3. Urine dipstick
   (UTI, vasculitis)
4. TFT and autoantibodies
Diagnosis of Chronic Urticaria

2. Special Investigations

- Further investigations as guided by history
- Symptom diary may be useful before embarking on extensive and expensive testing
Further Investigations

- A. Directed allergy testing
- Skin Prick Tests useful of any suspicion of allergen triggers
  - Visual and at point of care
  - Usually disproves the suspicion
- CAST tests for preservatives only if a high suspicion
Further Investigations

- B. For suspected vasculitis/connective tissue disease
- ANA, anti-DS DNA
- Biopsy of suspected vasculitis lesions
Further Investigations

C. Provocation (challenge) testing

- Ice cube test
- Submersion of a limb in water (hot/cold)
- Exercise
Further Investigations

• C. Provocation (challenge) testing
  ◦ Ice cube test
Further Investigations

- **D. Tests of autoimmunity**
  - Autologous serum skin test
  - Anti IgE antibodies
Further Investigations

- E. Hereditary angioedema screening
  - In isolated angioedema
  - C4 levels (low in HAE)
  - C1 esterase inhibitor levels
  - C1 esterase function tests
Differentials

- Urticarial Vasculitis
- Cryoglobinaemia
- Cryopyrin associated periodic syndromes
- Polymorphic eruption of pregnancy
- Mastocytosis (condition with overproliferation and accumulation of tissue mast cells)
- Recurrent erythema multiforme
Treatment of Chronic Urticaria

1. Avoidance of Triggers

2. Control symptoms with second/third generation antihistamines (upward titration)

3. Consider other treatment options:
   - Sedating antihistamines at night
   - LTRA
   - Tranexamic acid for angioedema
   - Immune modulators
   - (Anti-IgE)
1. Avoidance of triggers

- Treat underlying infection/malignancy
- Avoid triggering allergens: NO BLANKET ELIMINATION DIETS
- Trial off possibly causative medications for several months
2. Second/third generation antihistamines

- Mainstay of treatment
- Active against H₁ receptor
- Better tolerated and fewer CNS side effects than 1st generation antihistamines
- Individual patients responses and side effects vary-
- May cause mild sedation hence patients should be advised to and excess alcohol and that performance of complex tasks may be affected- but generally very well tolerated
2. Second/third generation antihistamines: how to dose?

- Start with recommended daily dose for a few days to make sure that tolerated
- Incrementally increase the dose according to response up to 4X recommended dose
- Once treatment control established, continue treating 3-12 months (or longer) then gradual withdrawal
- For patient with infrequent symptoms, may be taken as required or prophylactically before special occasions
2. Second/third generation antihistamines: which drug?

- Loratadine
- Cetirizine
- Fexofenadine
- Desloratadine
- Levocetirizine

all licensed for CU
2. Second/third generation antihistamines: which drug?

- Very few comparator trials-
- Cetirizine seems to have the slight upper hand


- Combination of 2 non-sedating antihistamines may be tried if a single type inadequate, or a trial of a different non-sedating antihistamine
3. First generation anti-histamines

- Highly sedating and many side effects
- May be useful for short term addition to newer antihistamines to gain symptom control
- Not ideal long term
  - Hydroxyzine
  - Chlorphenamine
  - Promethazine
Sedating antihistamines ctd

**Doxepin**
- Doxepin is a tricyclic antidepressant which is useful in the treatment of antihistamine-resistant urticaria
- Dose range is 25-75mg daily
- High affinity for H₁ receptor (8x greater than diphenhydramine)
- Significant H₂ blocking activity
- Cautions:
  1. Never withdraw abruptly
  2. Do not administer concurrently with other anti-depressants
  3. Do not administer to patients with significant heart disease
  4. Possesses significant anti-muscarinic activity
Other treatment options

- Anti-histamines may not be entirely effective in controlling CU
- Variety of other cytokines which are not blocked by antihistamines may be involved:
  - Leukotrienes
  - Prostaglandin D2
  - Kinins
Other treatment options

1. Leukotriene receptor antagonists
   - Useful in combination with antihistamines in a subgroup of patients
   - Safe drug with rapid onset of action therefore worth a trial
   - Particularly useful in those with
     - chronic autoimmune urticaria
     - adverse response to NSAIDs/aspirin
     - delayed pressure urticaria
Other treatment options

2. H₂ receptor antagonists
   - Target histamine binding to the H₂ receptor
   - May provide marginal benefit in combination with H₁ receptor blockers
   - E.g ranitidine

   - Sharpe and Shuster. In dermographic urticaria H2 receptor antagonists have a small but therapeutically irrelevant effect compared with H1 antagonists alone. BJD 2006; 129: 575-9
Other treatment options

3. Corticosteroids
   - Short course of oral steroids can be added to antihistamines in severe cases or if rapid relief required
   - Long term low dose corticosteroids may be needed in stubborn cases
   - Useful for urticarial vasculitis
   - Significant systemic side effects
Other treatment options

4. Immune modulators
   - For severe unremitting disease uncontrolled by antihistamines
   - Most experience is with ciclosporin

Other treatment options

4. Ciclosporin
   - Can have rapid onset of action
   - Monitor BP and renal function
   - Treatment usually maintained for 3-6 months then slowly withdrawn
   - After ciclosporin withdrawal:
     - 1/3 excellent long term response
     - 1/3 mild relapse and can be maintained on anti-histamine;
     - 1/3 relapse and need to resume ciclosporin treatment
Other treatment options

5. Tranexamic acid
   - For severe angioedema
   - Inhibits conversion of plasminogen → plasmin (plasmin → bradykinin)
   - Also useful in prophylaxis for HAE cases
Other treatment options

6. Anti-IgE antibody (omalizumab)
   - Humanised anti IgE antibody, subcut injection
   - Early trials and case reports very promising
   - Rapid reduction in symptoms, then long term (6 month) relief after only one dose
     - Kaplan et al. JACI 2008; 122: 569-73
     - Goberet al JACI 2008; 121: S147
Other treatment options

- 7. IV immunoglobulin
  - 400 mg/kg for 5 days was shown to have good benefit in 9/10 patients with severe autoimmune CU.
  - 3/10 had long term benefit

  - O`Donnell et al BJD 1998; 138: 101-6)
Other treatment options

8. Adrenaline
   ◦ Never for isolated urticaria
   ◦ Only if severe angioedema affecting the upper airway
Other Treatment Options

9. Experimental treatment options:
   ◦ Nifedipine
   ◦ Colchicine
   ◦ Sulphasalazine
   ◦ Dapsone
   ◦ Methotrexate
Treatment algorithm:

1. Standard dose non sedating H₁ antihistamine
2. Higher dose (up to 4x) non sedating H₁ anti histamine or add a second non-sedating anti-histamine
3. Consider adding a sedating anti-histamine at night short term
4. Add second line agent eg LTRA, ranitidine and tranexamic acid (if predominantly angioedema)
5. Add or substitute ciclosporin, low dose Corticosteroid or anti IgE
Prognosis

- Duration of illness 2-10 years
- 25% have remission within the first 3 years
- 20% of adults with CU still have symptoms after 10 years
- Severity of illness, presence of angioedema, positive antithyroid antibodies, and positive ASST ↑ severity and persistence
Overall summary

- Chronic urticaria can be demoralising and disfiguring for the patient
- Up to 90% of cases of chronic urticaria are idiopathic or autoimmune
- Most cases are overinvestigated
- Food allergy is extremely rarely a trigger
- Spicy foods/ certain preservatives may trigger exacerbation but are not the primary cause
Overall summary

- An excellent history is the mainstay of diagnosis
- A basic batch of screening tests is recommended (FBC, ESR, TFT, Urine dip)
- Further tests are guided by the history and include allergen testing, provocation tests
- Don`t waste time on unproven and ineffective treatments and “allergy tests”
Overall summary

- Treatment is based on avoiding triggers and giving newer generation antihistamines at up to 2-4 x the recommended dose.
- Other treatment options including LTRA, ranitidine and ciclosporin are available and are added to antihistamines in resistant cases.
- Anti-IgE antibody holds much promise but is not yet available in SA
- When all else fails- revisit the diagnosis