Definitions

- **A wheal:**
  - Central swelling of variable size
  - Associated with itching or burning sensation
  - Fleeting nature. Skin returns to normal within 1-24 h

- **Angioedema:**
  - Sudden, pronounced erythematous or skin-coloured swelling of lower dermis & subcutis w frequent involvement below mucous membranes
  - Sometimes painful, rather than itchy.
  - Can take up to 72h for resolution
Definitions

- Chronic urticaria = frequent, mast-cell driven disease, presenting with wheals, angioedema or both
- Acute urticaria = < 6/52
- Lifetime prevalence approximately 20%
- Chronic spontaneous urticaria
  - decrease QOL
  - affect performance at work/school
Pathophysiology

- Mast-cell driven disease (activating signals not well defined)
- Histamine & other mediators eg. Platelet-activating factors, cytokines, released from activated mast cells
  - Sensory nerve activation
  - Vasodilatation
  - Plasma extravasation
- Histologically: oedema of upper & mid-dermis
  - Upregulation of endothelial cell adhesion molecules & mixed inflammatory perivascular infiltrate
Classification of urticarias

**Table 1** Classification of urticarias

<table>
<thead>
<tr>
<th>Chronic urticaria subtypes</th>
<th>Chronic inducible urticaria</th>
</tr>
</thead>
<tbody>
<tr>
<td>Chronic spontaneous urticaria</td>
<td>Physical urticaria</td>
</tr>
<tr>
<td>Spontaneous appearance of itchy wheals, angioedema, or both ≥6 weeks due to known* or unknown causes</td>
<td>Symptomatic dermographism†</td>
</tr>
<tr>
<td></td>
<td>Cold urticaria‡</td>
</tr>
<tr>
<td></td>
<td>Delayed pressure urticaria§</td>
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<tr>
<td></td>
<td>Solar urticaria</td>
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<tr>
<td></td>
<td>Heat urticaria¶</td>
</tr>
<tr>
<td></td>
<td>Vibratory angioedema</td>
</tr>
<tr>
<td>Other inducible urticaria</td>
<td>Other inducible urticaria</td>
</tr>
<tr>
<td>Cholinergic urticaria</td>
<td>Cholinergic urticaria</td>
</tr>
<tr>
<td>Contact urticaria</td>
<td>Contact urticaria</td>
</tr>
<tr>
<td>Aquagenic urticaria</td>
<td>Aquagenic urticaria</td>
</tr>
</tbody>
</table>

*For example, autoreactivity, that is, the presence of histamine-releasing autoantibodies; †also called urticaria factitia, dermographic urticaria; ‡also called cold contact urticaria; §also called pressure urticaria; ¶also called heat contact urticaria.
Assessment

- Time of onset of disease
- Frequency/duration & triggers (physical agents, exercise, drugs, foods)
- Diurnal variation
- Shape, size & distribution of wheals
- Associated angioedema
- Associated subjective symptoms of lesions
- Family & personal history of atopy
- Previous/current allergies, infections, medical history
- Psychosomatic/psychiatric diseases
- Surgical implantations/previous complications
- Gastrointestinal problems
- Relationship to menstrual cycle, stress
- Quality of life
### Disease Severity

**Table 4** The UAS7 for assessing disease activity in CSU

<table>
<thead>
<tr>
<th>Score</th>
<th>Wheals</th>
<th>Pruritus</th>
</tr>
</thead>
<tbody>
<tr>
<td>0</td>
<td>None</td>
<td>None</td>
</tr>
<tr>
<td>1</td>
<td>Mild (&lt;20 wheals/24 h)</td>
<td>Mild (present but not annoying or troublesome)</td>
</tr>
<tr>
<td>2</td>
<td>Moderate (20–50 wheals/24 h)</td>
<td>Moderate (troublesome but does not interfere with normal daily activity or sleep)</td>
</tr>
<tr>
<td>3</td>
<td>Intense (&gt;50 wheals/24 h or large confluent areas of wheals)</td>
<td>Intense (severe pruritus, which is sufficiently troublesome to interfere with normal daily activity or sleep)</td>
</tr>
</tbody>
</table>

Sum of score: 0–6 for each day is summarized over one week (maximum 42).
Differential Diagnosis

Table 3 Diseases related to urticaria for historical reasons and syndromes that present with hives and/or angioedema

- Maculopapular cutaneous mastocytosis (urticaria pigmentosa)
- Urticarial vasculitis
- Bradykinin-mediated angioedema (e.g., HAE)
- Exercise-induced anaphylaxis
- Cryopyrin-associated periodic syndromes (CAPS; urticarial rash, recurrent fever attacks, arthralgia or arthritis, eye inflammation, fatigue and headaches), that is, familial cold autoinflammatory syndrome (FCAS), Muckle–Wells syndrome (MWS), or neonatal onset multisystem inflammatory disease (NOMID).
- Schnitzler’s syndrome (recurrent urticarial rash and monoclonal gammopathy, recurrent fever attacks, bone and muscle pain, arthralgia or arthritis and lymphadenopathy
- Gleich’s syndrome (episodic angioedema with eosinophilia)
- Well’s syndrome (Granulomatous dermatitis with eosinophilia)

These diseases and syndromes are related to urticaria (i) because they present with wheals, angioedema, or both and/or (ii) because of historical reasons.
# Inducible Urticarias

## Table 2: Definition, frequency, and duration of ClndUs

<table>
<thead>
<tr>
<th>Definition</th>
<th>Frequency*</th>
<th>Duration*</th>
</tr>
</thead>
<tbody>
<tr>
<td>Symptomatic dermographism</td>
<td>Itching and/or burning skin and the development of strip-shaped wheals due to shear force acting on the skin</td>
<td>1-5% in the general population (10, 139–141)</td>
</tr>
<tr>
<td>Cold Urticaria</td>
<td>Itchy wheals or angioedema after cold exposure of the skin</td>
<td>Up to one-third of all PhysU cases (145)</td>
</tr>
<tr>
<td>Heat Urticaria</td>
<td>Itchy wheals after heat exposure of the skin</td>
<td>Very rare, no data available</td>
</tr>
<tr>
<td>Delayed Pressure Urticaria</td>
<td>Erythematous skin swelling after the application of sustained pressure</td>
<td>37% of patients with CSU (64) but rare as a primary inducible urticaria</td>
</tr>
<tr>
<td>Solar urticaria</td>
<td>Itchy wheals that occur after light (UV and/or visible light) exposure</td>
<td>Rare in general population, 0.08% of patients with CSU (75), 18% of patients who consult a hospital because of sunlight-related skin problems (147)</td>
</tr>
<tr>
<td>Vibratory angioedema</td>
<td>Cutaneous swellings immediately after exposure to vibration</td>
<td>Very rare, no data available</td>
</tr>
<tr>
<td>Cholinergic Urticaria</td>
<td>Itchy wheals after active or passive warming</td>
<td>4–11.2% of population (151–153)</td>
</tr>
<tr>
<td>Aquagenic urticaria</td>
<td>Itchy wheals or angioedema after skin contact with water</td>
<td>Very rare, no data available</td>
</tr>
<tr>
<td>Contact Urticaria</td>
<td>Itchy wheals or angioedema after contact with eliciting agent</td>
<td>Variable, depending on elicitor</td>
</tr>
</tbody>
</table>

*For most ClndUs, no reliable data on prevalence, incidence, and duration are available. The data presented are largely based on observational studies in small, preselected populations rather than from well-designed epidemiological studies.
Urticarial Vasculitis

• Continuum of disease:
  • Urticaria with minimal vasculitis to life-threatening systemic vasculitis with minimal urticaria

• Hypocomplementemic urticarial vasculitis syndrome
  • > 6 months of urticaria with hypocomplementaemia with systemic findings
    • Arthritis/arthralgias
    • Mild glomerulonephritis
    • Uveitis or episcleritis
    • Recurrent abdominal pain

• Hypocomplementaemic urticarial vasculitis
  • Do not meet criteria for HUVS
  • Generally have cutaneous disease & few/no systemic features
Cryopyrin-Associated Periodic Syndrome (CAPS)

- Autosomal dominant inheritance.

- Mutations in the NLRP3 gene (CIAS1 or PYPAF) encoding for cryopyrin
  - Crucial inflammasome protein that directly activates IL-1\(\beta\).

- Mutations induce an imbalance (excessive) in IL-1\(\beta\) production.
  - Leading to fever attacks associated with other multiple inflammatory symptoms.
    - Arthralgia, urticarial rash

- Three known forms of CAPS (overlapping severity spectrum).
  - Least severe is familial cold autoinflammatory syndrome (FCAS)
  - Medium severity is Muckle-Wells syndrome (MWS)
  - Severe - chronic infantile neurological cutaneous articular syndrome (CINCA/NOMID).

_Lachmann. Clinical and Experimental Immunology, 165: 301–309_
_Savic et al. Curr Opin Rheumatol 2012, 24:103–112_
Classical diffuse urticarial rash of CAPS. Slightly itchy and are often remarkably asymptomatic.

Urticarial rash in a 16-year-old girls with Muckle-Wells syndrome

Federici & Gattorno. Best Practice & Research Clinical Rheumatology 28 (2014) 263-276
Lachmann. Clinical and Experimental Immunology, 165: 301–309
HAE

- Excessive production of bradykinin (vasodilatory mediator)
  - Histamine & mast cells mediators not directly involved (no response to AH)

- Due to deficiency/dysfunction of C1 inhibitor
  - Impact on coagulation & complement cascades
  - 3rd type of HAE with normal C1INH levels
  - Autosomal dominant condition

- No urticaria

- Painful rather than itchy swelling

- GI disturbance with abdominal “attacks”

- Indications for screening:
  - Recurrent angioedema without urticaria
  - Unexplained recurrent episodes of self-limited, colicky, abdominal pain
  - Family history of angioedema
  - Unexplained laryngeal oedema
  - Low C4 levels in setting of angioedema
Investigation of urticaria
CIU Management

- Aim for complete symptom control
- Elimination/avoidance of trigger/stimulus
- Symptomatic pharmacological treatment by reducing mast cell mediator release and/or effect of these mediators at the target organ
- Induce tolerance
- Refer: on 20mg BD cetirizine AND taking it regularly

*Acute urticaria is self-limiting. Symptomatic treatment
# Mast cell disorders

<table>
<thead>
<tr>
<th>Primary mast cell activation disorders</th>
</tr>
</thead>
<tbody>
<tr>
<td>Mastocytosis (systemic and cutaneous)</td>
</tr>
<tr>
<td>Monoclonal mast cell activation syndrome (MMAS)</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Secondary mast cell cell activation disorders</th>
</tr>
</thead>
<tbody>
<tr>
<td>Allergic disorders (IgE-mediated hypersensitivity reactions)</td>
</tr>
<tr>
<td>Mast cell activation associated with chronic inflammatory or neoplastic disorders (mast cell hyperplasia)</td>
</tr>
<tr>
<td>Physical urticarias</td>
</tr>
<tr>
<td>Chronic autoimmune urticaria</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Idiopathic mast cell activation disorders</th>
</tr>
</thead>
<tbody>
<tr>
<td>Idiopathic anaphylaxis</td>
</tr>
<tr>
<td>Idiopathic urticaria</td>
</tr>
<tr>
<td>Idiopathic angioedema</td>
</tr>
<tr>
<td>Mast cell activation syndrome (MCAS)</td>
</tr>
</tbody>
</table>
Diagnostic Approach

• Attribution of signs/symptoms to a mast cell activation disorder if the following 3 criteria are met
  1. Typical signs and symptoms of mast cell mediator release
     • Skin
     • CVS
     • Respiratory
     • GIT
  2. Objective evidence of mediator release
     • Elevated serum tryptase
       ○ 20% + 2ng/ml above baseline
     • Elevated 24-hour urinary histamine metabolites (methylhistamine)
     • Elevated 24-hour urinary prostaglandins
  3. Response to therapy that blocks mast cell mediator activity
     • H1-receptor blocker
     • Cromolyn sodium
     • Aspirin
     • Leukotriene receptor antagonists
Primary mast cell activation disorders

- Associated with intrinsic defects in mast cells affecting proliferation or activation pathways
  - Clonal populations of mast cells arise from an affected progenitor
  - Display abnormal genetic & surface markers

- Stem cell factor critical for mast cell growth & differentiation
  - Transmembrane receptor for SCF is KIT (encoded by proto-oncogene c-kit)
Mastocytosis

- Systemic Mastocytosis
  - Episodes of symptoms caused by mast cell-mediator release, lasts minutes to hours
  - Flushing
  - GI cramping
  - Hypotension
  - Urticaria pigmentosa (80%)

- Can have MSK/neuropsychiatric symptoms

- Some patients present with anaphylaxis to hymenoptera stings

- >90% have point mutation in exon 17 of c-kit gene

- Diagnosis:
  - WHO diagnostic major/minor criteria
  - Bone marrow mast cell infiltrate
  - Mast cell surface expression of CD25 and/or CD2
  - Serum total tryptase > 20 ng/mL
  - Identification of c-Kit mutation

- Cutaneous mastocytosis: signs & symptoms with UP & findings on skin biopsy. Normal bone marrow studies.
Secondary mast cell activation disorders

- Mast cells are normal in quantity & function
  - Responding to an external stimulus

- Include:
  - Allergic diseases (IgE mediated allergy)
  - Types of physical & contact urticaria
  - Autoimmune urticaria
  - Neoplastic & haematological disorders
    - Reactive mast cells have mature appearance & lack surface marker abnormalities in primary MCD
    - Breast ca, Hodkin lymphoma, skin & connective tissue tumours
    - Aplastic anaemia
Idiopathic mast cell activation

- No identifiable cause of mast cell activation
- Includes CIU, idiopathic angioedema & anaphylaxis
- Mast cell activation syndrome
  - Episodic symptoms of mast cell mediator release affecting > 2 organ symptoms
  - Increased mast cell activation during a symptomatic period
- May be shown to be primary MCD in future as new genetic mutations are found
### Comparison of clinical and diagnostic features for systemic mastocytosis, mast cell activation syndromes, and idiopathic anaphylaxis

<table>
<thead>
<tr>
<th></th>
<th>Systemic mastocytosis</th>
<th>Monoclonal mast cell activation syndrome (MMAS)</th>
<th>Mast cell activation syndrome (MCAS)</th>
<th>Idiopathic anaphylaxis</th>
</tr>
</thead>
<tbody>
<tr>
<td>Baseline tryptase*</td>
<td>&gt;20</td>
<td>Normal or mildly increased</td>
<td>Normal or mildly increased</td>
<td>Normal</td>
</tr>
<tr>
<td>kit D816V</td>
<td>+</td>
<td>+</td>
<td>–</td>
<td>–</td>
</tr>
<tr>
<td>Multifocal mast cell aggregates</td>
<td>+</td>
<td>–</td>
<td>–</td>
<td>–</td>
</tr>
<tr>
<td>Aberrant CD25</td>
<td>+</td>
<td>+</td>
<td>–</td>
<td>–</td>
</tr>
<tr>
<td>Urticaria pigmentosa</td>
<td>+/-</td>
<td>–</td>
<td>–</td>
<td>–</td>
</tr>
<tr>
<td>Mediator-release symptoms</td>
<td>+</td>
<td>+</td>
<td>+</td>
<td>+</td>
</tr>
<tr>
<td>Hypotensive episodes</td>
<td>+/-</td>
<td>+/-</td>
<td>+/-</td>
<td>+/-</td>
</tr>
<tr>
<td>Urine N-MH or PGD₂</td>
<td>Increased at baseline</td>
<td>Increased during symptoms</td>
<td>Increased during symptoms</td>
<td>Increased during symptoms</td>
</tr>
<tr>
<td>Response to ant mediatoer therapy</td>
<td>+</td>
<td>+</td>
<td>+</td>
<td>+/-</td>
</tr>
</tbody>
</table>

N-MH: N-methylhistamine; PGD₂: prostaglandin D₂.  
* Elevations in serum tryptase corresponding to symptoms (particularly hypotension) may be seen in all four disorders. Increases in tryptase greater than 1.2 x baseline value + 2 ng/mL are considered significant. For example, if a patient’s baseline total tryptase was 5 ng/mL, a value of 8 ng/mL would represent a significant increase.
Familial Tryptasaemia

- Persistent elevations in serum basal tryptase levels in absence of evidence for a clonal mast cell disorder
- Do not meet WHO criteria for SM
- Autosomal dominant inheritance pattern
- Symptoms consistent with chronic & episode mast cell degranulation
  - Episodic urticaria
  - Flushing
  - Cramping abdominal pain a/w urgency/diarrhoea
  - Anaphylaxis
- Can be unprovoked or triggered by heat, exercise, vibration, emotional stress, non-specific foods or minor physical trauma

Lyons et al. JACI May 2014. 133 (5)
Diagnostic Algorithm

Figure. Diagnostic algorithm for mast cell activation disorders. AHNMD = associated hematologic non-mast cell lineage disease; MCA = mast cell activation; MCAD = mast cell activation disorder; MCAS = mast cell activation syndrome; MMAS = monoclonal mast cell activation syndrome; SM = systemic mastocytosis.
Management

- Symptomatic treatment. No cure
- Avoidance of triggers
- Medications chosen on basis of symptoms
  - H1 antihistamines: urticaria, pruritis
  - H2 antihistamines, cromolyns: GI symptoms
  - Leukotriene-receptor antagonists: bronchospasms, flushing, itch, abdominal cramping
  - Aspirin: flushing
- Need Epipen if anaphylaxis
- Omalizumab: successful reports
Familial cold auto-inflammatory syndrome (FCAS)

- Milder end of the spectrum of CAPS.
- Appears during the first few months of life.
- Recurrent flares of low-grade fever triggered by cold exposure (93%).
  - Also polyarthralgia (96%) and urticarial rash (100%)
  - Start 1 to 2 hours after exposure to cold and last 12 to 48 hours.
- Other symptoms:
  - Conjunctivitis (84%), profuse sweating (78%), dizziness (67%), headache (58%), nausea (51%) and excessive thirst (53%).
- Definitive diagnosis - genetic mutations in NLRP3.
- Secondary amyloidosis can occur in 2% of the cases.

Caso et. Al International Journal of Rheumatology Volume 2013, Article ID 513782
Muckle-Wells syndrome (MWS)

- Present in childhood with urticarial rash, low-grade fever and arthralgia.
- Recurrent arthritis and conjunctivitis episodes frequently occur.
- During severe attacks, headache, and papilledema can occur (aseptic meningitis).
- Sensorineural hearing loss is the most typical clinical feature in MWS
  - Due to chronic inflammation of the inner ear.
- Secondary amyloidosis is frequently observed.
  - Affects 25 to 33% of the untreated patient.
- Abnormal laboratory findings
  - Marked leucocytosis, neutrophilia, thrombocytosis, anaemia
  - Increased ESR and CRP.
- Diagnosis
  - Mutations in NLRP3.
  - Clinically – consider MWS in patients with classical neutrophilic urticarial and familial disease.

Caso et. Al International Journal of Rheumatology Volume 2013, Article ID 513782
Neonatal-onset multisystem inflammatory disease (NOMID)/
Chronic infantile neurologic cutaneous and articular syndrome (CINCA)

• Most severe end of the CAPS spectrum

• Low-grade fever, cutaneous rash, aseptic meningitis and arthropathy, in the first weeks of life.

• Neurological involvement is a diagnostic feature of NOMID
  • Chronic aseptic neutrophilic meningitis
  • Chronic irritability, headache, seizures, transitory hemiplegia and rarely lower limb spasticity.

• If untreated, NOMID patients develop permanent organ damage:
  • Consequence of persistent inflammation in the affected organs.
  • Cochlear inflammation leads to sensorineural hearing loss.
  • Chronic aseptic meningitis leads to increased intracranial pressures and hydrocephalus, brain atrophy, and chronic papilledema that leads to optic nerve atrophy and progressive vision loss.
  • Inflammatory eye manifestation leads to conjunctivitis.

• Patients with hydrocephalus - “typical facies” with frontal bossing, large cephalic perimeter and “saddleback” nose.

• Cognitive delay is multifactorial
  • Due to perinatal insult, and the degree of CNS inflammation and brain atrophy.
NOMID

• Treatment
  • IL-1 blocking agents (anakinra, rilonacept or canakinumab)
  • Recombinant IL1R antagonist (anakinra) - used for NOMID treatment for over 10 years
  • Rapid response to anakinra with dramatic improvement of inflammatory symptoms, fever, skin rash, and acute phase reactants.

A) Characteristic facies (saddle nose) and urticaria-like rash of neonatal onset multisystem inflammatory disease