Evaluation and management of urticaria

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Disclosures

- I do not have any relevant financial or commercial interests to disclose.
- I do not intend to discuss an unapproved or investigative use of a commercial product/device in my presentation.

Learning objectives

- To discuss the differential diagnosis of acute urticaria
- To deepen our understanding surrounding the evaluation and management of acute urticaria
- To discuss the differential diagnosis of chronic urticaria
- To deepen our understanding surrounding the evaluation and management of chronic urticaria

Clinical case #1

- A previously healthy 3-year-old female who presented to clinic for an initial evaluation of urticaria.
- Reports a 4-week history of urticaria which is worse with heat exposure.
- Dad denies worsening symptoms with cold exposure, pressure, or NSAID use and denies bruising after hives resolve.
- Hives resolve on their own within a few hours.
- She started taking Zyrtec 2.5 mg daily and her hives have now resolved.

Clinical case #2

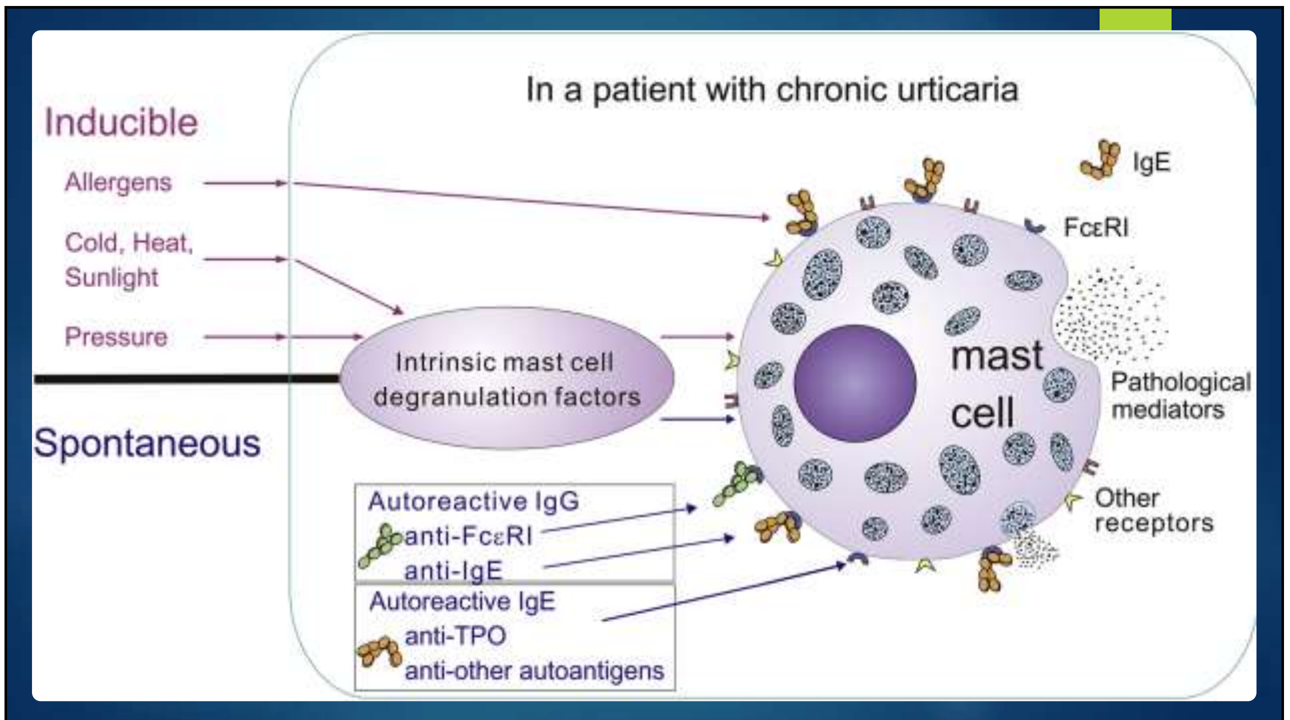
- A 55 y.o. female with history of pre-diabetes, hypertension, GERD, hypothyroidism, and chronic hives who presented to clinic for an initial evaluation of chronic urticaria.
- Reports daily hives for almost 5 years despite taking prednisone 20 mg daily. In addition, she is also taking famotidine 20 mg daily and Singulair 10 mg daily. She denies bruising after her hives resolve.
- She was initially started on Zyrtec 20 mg twice daily with improvement in her symptoms. However, she was unable to wean off prednisone.
- Given that her hives have persisted while taking prednisone, she was evaluated by Dermatology to rule out urticarial vasculitis; however, she did not have hives at her visit and therefore a biopsy was not performed.
- At subsequent visit, she was started on Omalizumab 300 mg monthly and has been able to wean steroids.

Introduction

- Acute urticaria: recurrent urticaria +/- angioedema for <6 weeks.
- Chronic spontaneous urticaria (CSU): recurrent urticaria +/- angioedema ≥ 6 weeks.
- For 80-90% of patients, no external cause is identified.

Classification of urticaria

- Duration:
  - Acute (< 6 weeks) or Chronic (≥6 weeks)
- Eliciting factors:
  - Inducible: specific eliciting factor involved
    - Symptomatic dermographism
    - Cold urticaria
    - Delayed pressure urticaria
    - Solar urticaria
    - Heat urticaria
    - Vibratory urticaria
    - Cholinergic urticaria
    - Contact urticaria
    - Aquagenic urticaria
  - Spontaneous: no specific eliciting factor involved

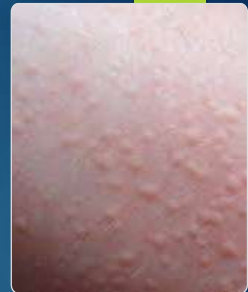
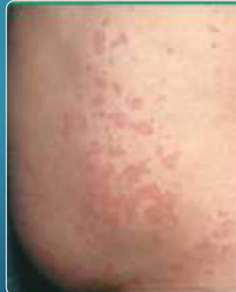
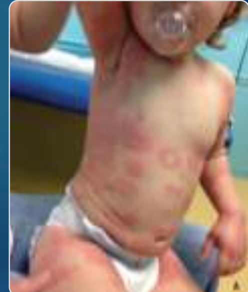


In a patient with chronic urticaria
Inducible
Allergens
Cold, Heat, Sunlight
Pressure
Intrinsic mast cell degranulation factors
Spontaneous
Autoreactive IgG
anti-FcεRI
anti-IgE
Autoreactive IgE
anti-TPO
anti-other autoantigens
mast cell
IgE
FcεRI
Pathological mediators
Other receptors

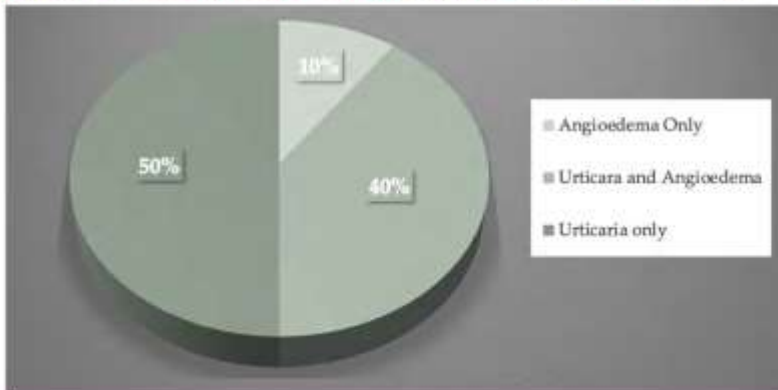
Clinical Manifestations

- Urticaria:
  - an area of central swelling of various size, usually with surrounding erythema
  - pruritus
  - individual lesion usually last 30 minutes to 24 hours with the skin returning to normal without bruising
- Angioedema:
  - a sudden, pronounced erythematous or skin colored swelling of the lower dermis or mucous membranes
  - sometimes pain, rather than pruritic
  - resolution can take up to 72 hours

Examples of urticaria

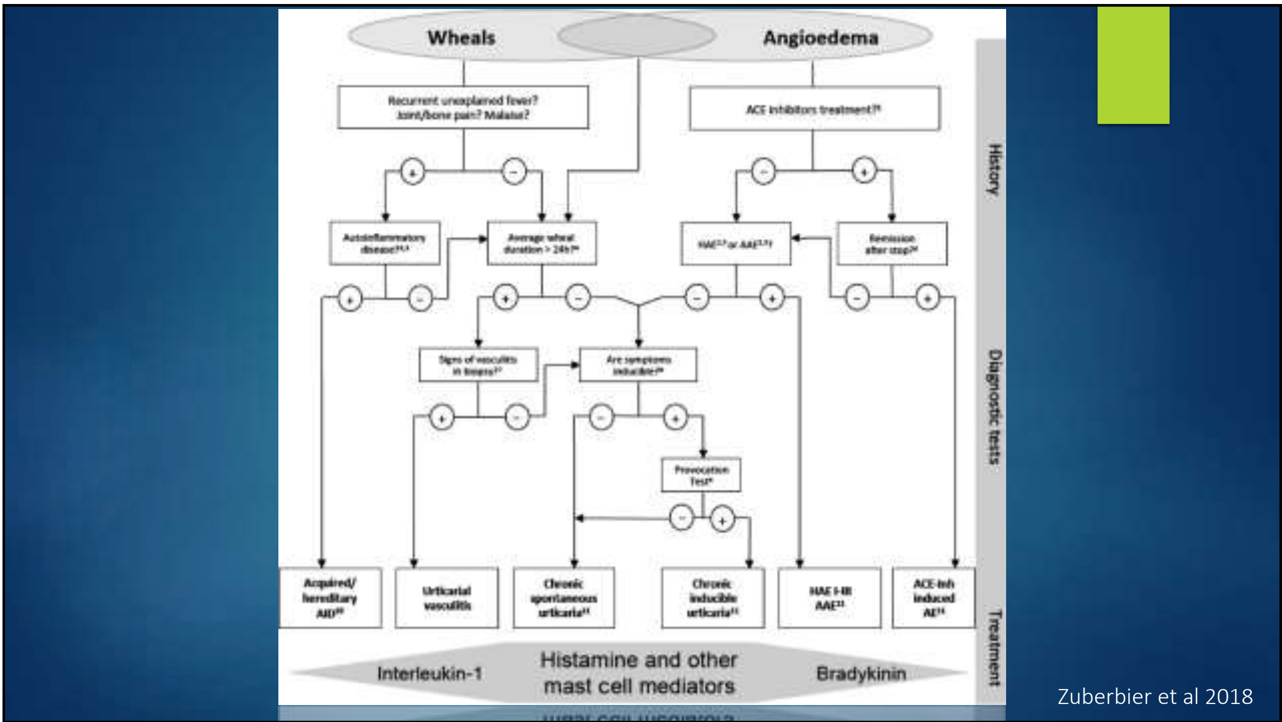
Dermographism



Clinical Presentation: Urticaria and Angioedema
10%
50%
40%
Angioedema Only
Urticara and Angioedema
Urticaria only
ACAAI/AAAAI ONLINE Joint Board Certification Review Course

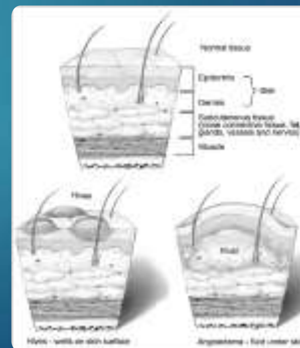
Clinical history

- Time of onset of disease, frequency/duration, inducible factors, and accompanying angioedema
  - *Does it itch?*
- **Systemic symptoms:** Fever, weight loss, arthralgias, arthritis, cold or heat sensitivity, abdominal pain, and bone pain
- **Triggers:** Foods, drugs (NSAIDs, ACEi), or menstrual cycle
- Previous therapy, response to therapy including dose/duration, and diagnostic procedures/results
- **PMH:** previous or current allergies, infections, autoimmune disease
- **FH:** Urticaria, angioedema, or autoimmune disease


Wheals
Angioedema
ACE inhibitors treatment?
History
Diagnostic tests
Provocation Test
Acquired/ hereditary AID
Urticarial vasculitis
Chronic spontaneous urticaria
Chronic inducible urticaria
ACE-Inh induced AE
Treatment
Interleukin-1
Histamine and other mast cell mediators
Bradykinin
Zuberbier et al 2018

Pathophysiology

- Histamine, platelet-activating factor (PAF), and cytokines are released from mast cells resulting in sensory nerve activation, vasodilation, plasma extravasation and cell recruitment.
- Wheals: edema of upper and mid dermis with dilation and augmented permeability of the postcapillary venules, as well as lymphatic vessels of the upper dermis.
- Angioedema: similar changes but in lower dermis or subcutis.



Common Causes of Acute Urticaria

- IgE mediated allergy
  - Food, medication, insect stings
- Exacerbation of physical urticaria
  - cold urticaria, cholinergic urticaria
- Non-IgE mediated medications
  - NSAIDs, opioids
- Papular urticaria caused by bug bites
  - fleas, scabies, bed bugs
- Infection
  - parvovirus B19, EBV, other viral

Bernstein et al. J Allergy Clin Immunol 2014

Chronic spontaneous urticaria (CSU) epidemiology

- CSU affects up to 1% of the general population in the United States.
- Both children and adults can develop CSU, although it is more common in adults.
- Women are affected twice as often as men and the condition typically begins in the third to fifth decades of life.

Associated conditions

- Strong association with atopic disorders which was demonstrated in a large cohort study of over 1 million Israeli adolescents. These associations were not seen in the adult population, when studied by the same researchers. Instead, an association with autoimmune conditions was observed.
- Various autoimmune conditions are more prevalent among patients with CSU such as thyroid disorders, celiac disease, Sjögren syndrome, systemic lupus erythematosus, rheumatoid arthritis, and type 1 diabetes mellitus.

Thyroid disorders

- In a study published from Israel in 2012, hypothyroidism was diagnosed in 9.8% of CSU patients (versus 0.6% of controls) and hyperthyroidism in 2.6% (versus 0.5% of controls).

- A population-based Korean study found that individuals with autoimmune thyroid disease (Hashimoto thyroiditis and Graves' disease) had higher rates of CSU compared with controls.

- Thyroid autoantibodies are more prevalent among patients with CSU (12-30%), compared with those of the general population (5-10%).

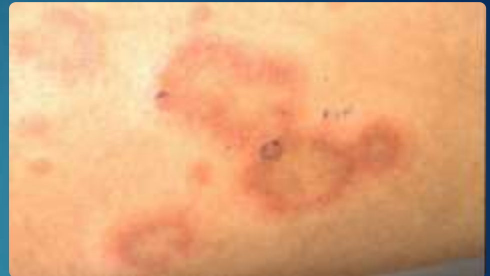
Differential Diagnosis

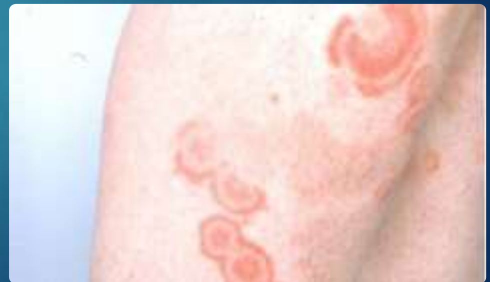
- *Urticarial vasculitis*
- Systemic lupus erythematosus
- Cryoglobulinemia
- *Schnitzler syndrome*
- *Mast cell disorders*
- Polymorphic eruption of pregnancy
- Hypereosinophilic syndrome
- Cryopyrin-associated periodic syndromes

Urticarial vasculitis

- Hives are painful rather than pruritic, last longer than 48 hours, leave residual bruising or pigmentation changes or recur whenever glucocorticoids are tapered.
- In addition, patients may report fever, chills and arthralgias.
- May occur in isolation or in patients previously diagnosed with other systemic inflammatory diseases, such as Sjögren syndrome or systemic lupus erythematous.
- Skin biopsy is indicated if signs or symptoms of vasculitis are present.

Urticarial vasculitis





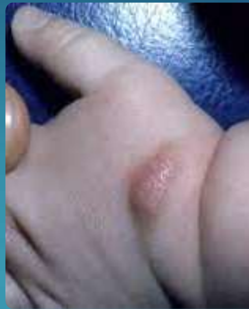
Schnitzler syndrome

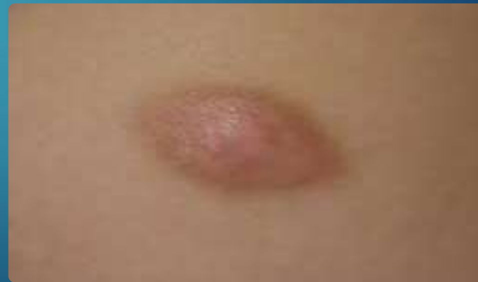
- These patients present with urticaria, recurrent fever, bone and muscle pain, lymphadenopathy, arthralgia, arthritis, weight loss and monoclonal gammopathy.
- This is presumably due to circulating immune complexes and complement activation.

Mast cell disorders

- Characterized by the proliferation and accumulation of tissue mast cells or excessive activity of these cells.
- Examples include systemic and cutaneous mastocytosis.
  - Skin findings include flushing, pruritus, or a distinctive lesion called urticaria pigmentosa.

Mastocytoma





https://dermnetnz.org/topics/mastocytosis

Quality of life

- Patients report that urticaria affects their functioning and well-being.
- O'Donnell et al showed that health scores in chronic spontaneous urticaria patients are comparable to patients with coronary artery disease.

The Urticaria Control Test

1. How much have you suffered from the **physical symptoms of the urticaria (itch, hives (welts) and/or swelling)** in the last four weeks?

O very much (0 points)	O much (1 point)	O somewhat (2 points)	O a little (3 points)	O not at all (4 points)

2. How much was your **quality of life** affected by the urticaria in the last 4 weeks?

O very much (0 points)	O much (1 point)	O somewhat (2 points)	O a little (3 points)	O not at all (4 points)

3. How often was the **treatment** for your urticaria in the last 4 weeks **not enough** to control your urticaria symptoms?

O very often (0 points)	O often (1 point)	O sometimes (2 points)	O seldom (3 points)	O not at all (4 points)

4. **Overall**, how well have you had your urticaria **under control** in the last 4 weeks?

O not at all (0 points)	O a little (1 point)	O somewhat (2 points)	O well (3 points)	O very well (4 points)

Weller et al. Journal of The European Academy of Dermatology and Venereology 2015

Urticaria Activity Score (UAS7)

Score	Hives (wheals)	Score	Itch Severity Score (ISS)
0	None	0	None
1	Mild (<20 hives/24 h)	1	Mild (present, but not annoying or troublesome)
2	Moderate (20–50 hives/24 h	2	Moderate (troublesome, but does not interfere with normal daily activity or sleep)
3	Intense (50 hives/24 h or large confluent areas of hives)	3	Intense (severe itch, which is sufficiently troublesome to interfere with normal daily activity or sleep)

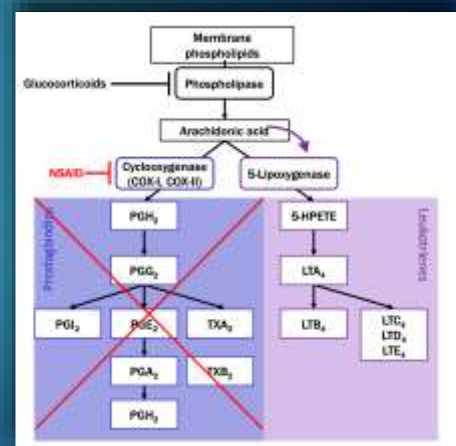
Zuberbier 2014

Natural history

- CSU is an episodic and self-limited disorder in most patients. The average duration of disease is 2-5 years.
- 40% of patients will have urticaria with angioedema.
- In patients in whom no trigger or underlying disorder is identified
  - In 40% of patients, they will have resolution of hives within 1 year
  - In 90% of patients, they will have resolution of hives within 5 years
- Remission rates in children may be higher.

NSAID-induced urticaria/angioedema in otherwise asymptomatic individuals

- Patients without underlying chronic urticaria develop acute urticaria +/- angioedema 30 to 90 minutes after ingestion of COX-1-inhibiting NSAIDs.
- Mechanism: COX-1 inhibition --> react to their very first dose of a COX-1 inhibitor and to structurally different COX-1-inhibiting NSAIDs.
- Usually tolerate highly selective COX-2-inhibiting NSAIDs (meloxicam)



Wohrl, S. Allergo Journal International 2017

NSAID-induced urticaria/angioedema in patients with chronic urticaria

- Patients with chronic urticaria can have an exacerbation, beginning 30 to 90 minutes after taking ASA/NSAIDs that inhibit COX-1.

- In 30% of patients with stable chronic urticaria, NSAIDs can exacerbate their hives- usually dose-dependent.

Diagnostic evaluation in acute urticaria

- Since it is usually self-limiting, further diagnostic evaluation is not warranted.
- Exception is IgE-mediated food allergy and NSAIDs as eliciting factor
  - Allergy tests and education to avoid re-exposure to relevant causative factors.

Diagnostic evaluation in CSU

- Exclude other causes
- Assess disease activity, impact, and control
- Identify triggers of exacerbation
- If there are no systemic symptoms, we do not typically obtain initial laboratory evaluation.
- Immediate hypersensitivity testing to environmental and food allergens is not warranted
  - *Diagnostic tests:*
    - thyroid gland disorders: TSH, free T4, and auto-antibodies
    - autoimmune urticaria: IgE-receptor antibody level, ESR/CRP
    - mast cell activation syndrome: tryptase
    - malignancy: CBC with differential, serum protein electrophoresis
    - urticarial vasculitis: C3 and C4
    - Skin biopsy: if concern for vasculitis

Diagnostic evaluation in chronic inducible urticaria

Provocation tests for inducible urticaria

Symptomatic dermographism (Urticaria factitia)

Testsite: Volar forearm or upper back
Test: Moderate stroking of the skin with a blunt smooth object (e.g. closed ballpoint pen tip, wooden spatula), dermographic tester (36 g/mm²), or FricTest (longest pin)
Reading time: 10 minutes after testing

W	I

Date / Time ____________ Test done by ____________
Positive test = wheal & itch: Test trigger strength threshold →

Cold urticaria

Testsite: Volar forearm
Test: Melting ice cube in thin plastic bag, TempTest (4-44°C) for 5 minutes
Reading times: 10 minutes after testing

W

Date / Time ____________ Test done by ____________
Positive test = wheal: Test temperature threshold →

Heat urticaria

Testsite: Volar forearm
Test: Heat source, TempTest (44.4 °C) for 5 minutes
Reading times: 10 minutes after testing

W

Date / Time ____________ Test done by ____________
Positive test = wheal: Test temperature threshold →

Delayed pressure urticaria

Testsite: Shoulder or upper back or thighs or volar forearm
Test: Suspension of weights over shoulder (7 kg, shoulder strap width: 3 cm) for 15 min or weighted rods (1.5 cm diameter: 2.5 kg; or 6.5 cm diameter: 5 kg) for 15 min. Dermographic tester at 100 g/mm² for 70 sec
Reading times: ~6 hours after testing

A	E

Date / Time ____________ Test done by ____________
Positive test = angio-edema & erythema: Test trigger strength threshold →

Solar urticaria

Testsite: Buttocks
Test: UVA 6 J/cm² & UVB 60 mJ/cm² (e. g. Saalmann Multitester SBC LT 400) & visible light (projector)
Reading times: 10 min after testing

	W
UVA	
UVB	
Visible light	

Date / Time ____________ Test done by ____________
Positive test = wheal: Test trigger strength threshold (UVA / UVB) →

Vibratory angio-edema

Testsite: Volar forearm
Test: Vortex vibrator for 5 minutes, 1000 rpm
Reading times: 10 minutes after testing

A	W

Date / Time ____________ Test done by ____________
Positive test = angio-edema or wheal

Cholinergic Urticaria

Management

- The goal of treatment depends on each patient. Treatment will improve quality of life by decreasing frequency of pruritus, urticaria, and angioedema.
- The therapeutic approach to CIU can involve:
  - Reassurance
  - Patient education
  - Avoidance of known triggers
  - Pharmacotherapy to prevent mast cell mediator release and/or the effects of mast cell mediators

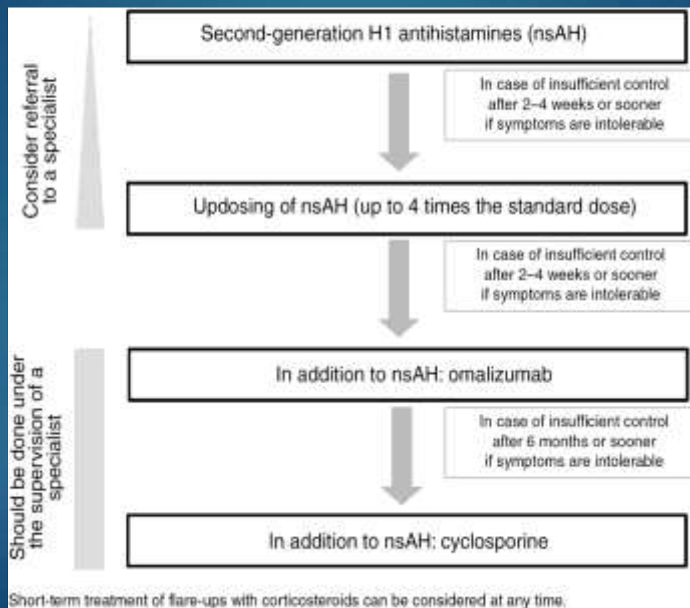
Elimination of underlying causes and avoidance of eliciting factors

- *Drugs:*
  - NSAIDs
- *Physical stimuli:*
  - For dermographism, reducing friction
  - For pressure-induced, broaden the handle of heavy bags
  - For cold urticaria, impact of wind chill factor
  - For solar urticaria, appropriate selection of sunscreens or for selection of light bulbs with a UV-A filter

Therapy course

- The severity of urticaria may fluctuate.
- Spontaneous remission may occur at any time, it is recommended to re-evaluate the necessity for continued or alternative drug treatment every 3-6 months.

Chronic spontaneous urticaria treatment



Zuberbier et al 2018

Chronic inducible urticaria treatment

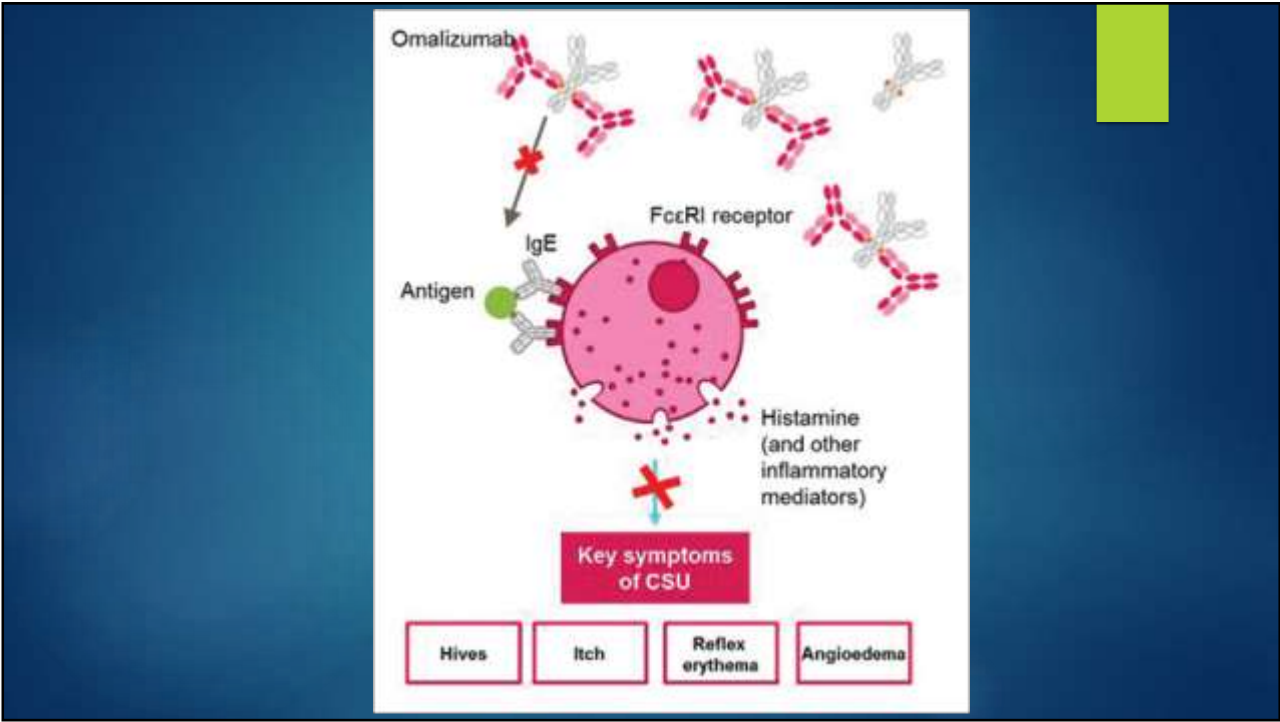
- Cold urticaria: might be better for on-demand treatment than continuous treatment.
  - For example, if expected cold exposure when going swimming then recommend taking anti-histamines 2 hours prior to activity

Anti-histamine refractory treatment

- Omalizumab has been shown to be very effective and safe in treatment of CSU.
- It has also been reported to be effective in chronic inducible urticaria.
- In CSU, omalizumab prevents development of angioedema, improves quality of life and is suitable for long-term treatment.

Omalizumab

- Mechanism: Recombinant, humanized, monoclonal antibody (mAb) against IgE that is approved for the treatment of antihistamine-resistant CSU in patients 12 years or older.
- Omalizumab 150 to 300 mg per month
- Dosing is independent of total serum IgE or body weight


Omalizumab
FcεRI receptor
IgE
Antigen
Histamine
(and other
inflammatory
mediators)
Key symptoms
of CSU
Hives
Itch
Reflex
erythema
Angioedema

Cyclosporine A

- Mechanism: Calcineurin inhibitors block the calcium-dependent release of and responsiveness to histamine, leukotriene C4, and other mediators in mast cells.
- Direct effect on mast cell mediator release.
- Given the higher incidence of adverse effects, it is only recommended for patients with severe refractory urticaria without improvement with high dose oral antihistamines and omalizumab.

Leukotriene antagonist

Previous randomized controlled trials have assessed the use of leukotriene antagonists.

Level of evidence for efficacy is low but best for montelukast.

Topical corticosteroids

- In urticaria, topical steroids are not helpful with a possible exception of pressure urticaria on the soles used as an alternative therapy.

Systemic corticosteroids

- If systemic corticosteroids are used, doses between 20 and 50 mg/day for prednisone are required with obligatory side effects on long-term use.
- There is a strong recommendation against the long-term use of corticosteroids outside specialist clinics.
- For acute urticaria and acute exacerbations of CSU, a short course of oral corticosteroids is sometimes prescribed.
- However, after patients complete the steroid course, they can have exacerbation of their urticaria.

Treatment of pediatric patients

- Discourage the use of first-generation antihistamines in infants and children.
- The same first-line treatment and up-dosing (weight and age adjusted) is recommended in children as in adults.
- Cetirizine, desloratadine, fexofenadine, levocetirizine, and loratadine have been well studied in children and their long-term safety has been well established in the pediatric population.

Treatment for pregnant women and lactating women

- No reports of birth defects in women taking 2nd-generation antihistamines during pregnancy has been reported to date.
- All H1-antihistamines are excreted in breast milk in low concentrations.
- 2nd-generation antihistamines are advised, as nursing infants can become sedated from first-generation H1-antihistamines transmitted in breast milk.
- Omalizumab: Proven to be safe and to date there is no indication of teratogenicity.
- Cyclosporine: Not teratogenic--> in animal models it was embryotoxic and has been associated with preterm delivery and low birth weight in human infants.

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