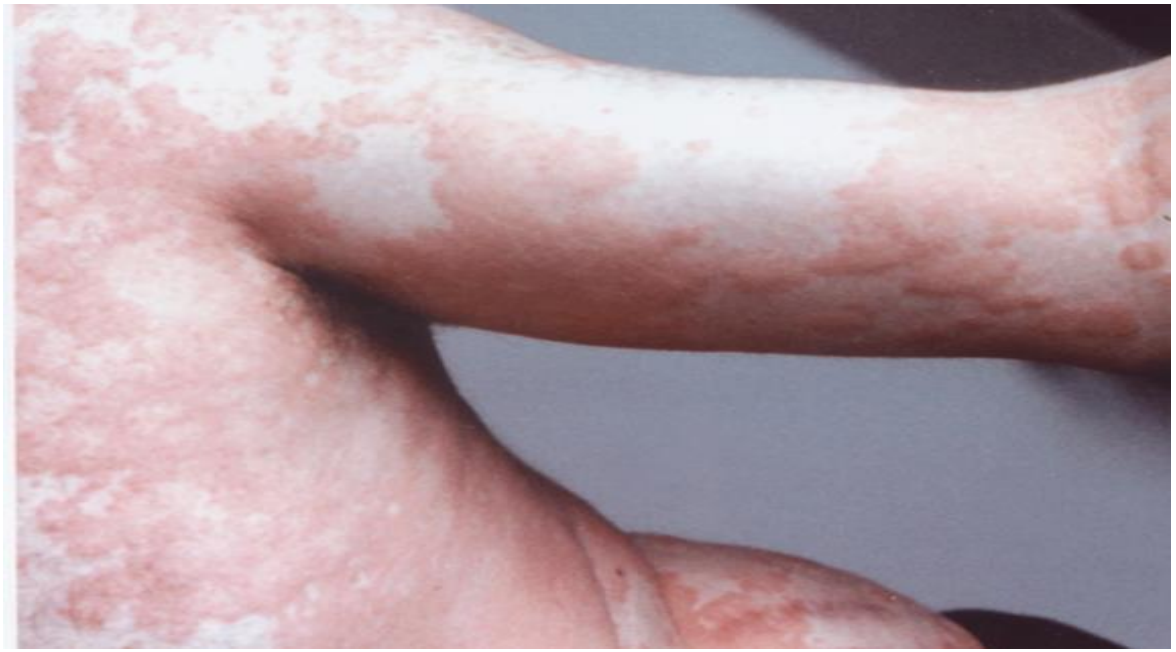
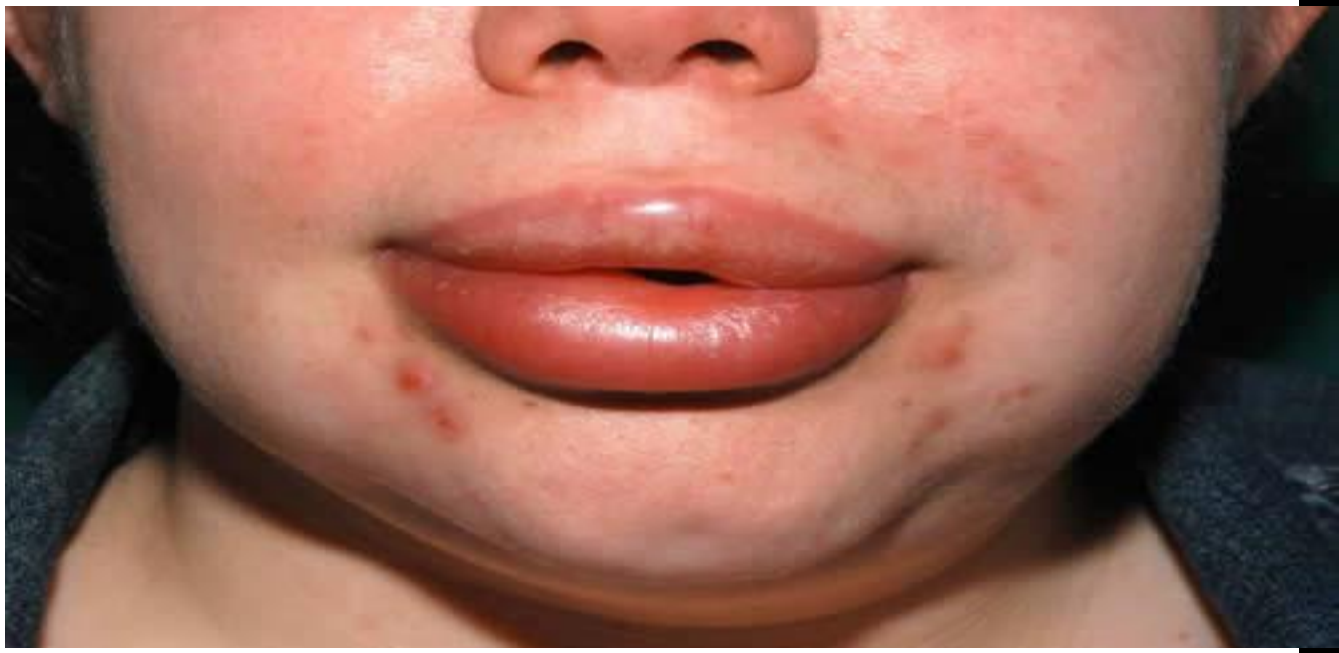
Urticaria and Angioedema





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The history of urticaria

The School of Hippocrates (4th century BC) already recognized the association of urticaria with *nettles* (Fig. 1), and this word was subsequently incorporated into the name used for urticaria in several languages. The Roman School focused instead on the sensation of burning (*urere*) at sites of wheals, and Plinius introduced the name *uredo*.

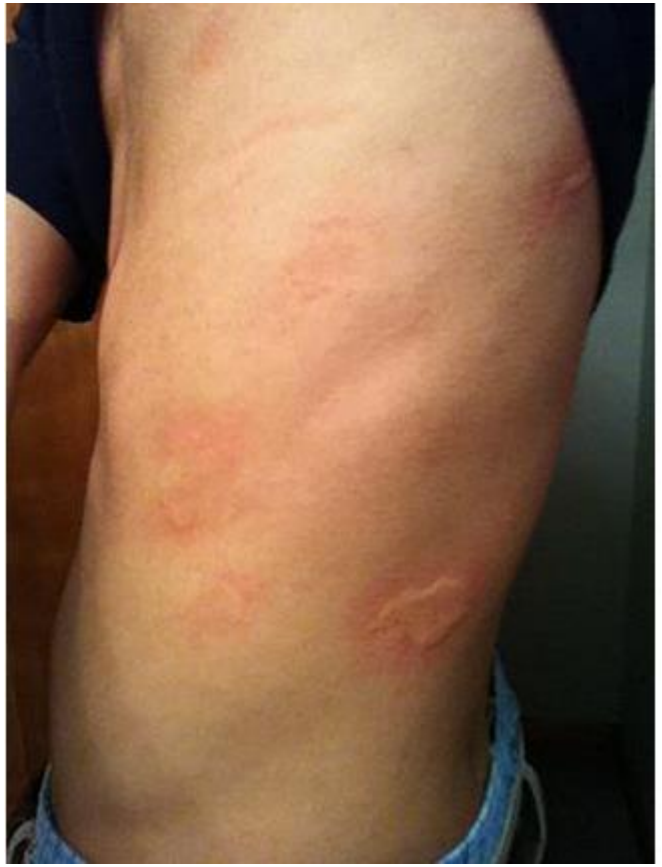
FIG. 1. Photograph of the nettle plant from which the name urticaria derives. The ability of the plant to cause whealing reactions on contact with skin was known already in antiquity. The reason for the elicitation of the wheal, namely, the injection of histamine and leukotrienes from the hairs of the nettle into the skin, has been known only since this century.

The history of urticaria

In the 10th century, Hali Ben Abbas used the name *essera,* meaning mountain or elevation, alluding to the elevation of the wheal above skin level. This name was in use in the medical literature until the end of the last century. In the 18th century, Zedler called the disease *urticatio,* and in 1792, Frank used the now commonly accepted name *urticaria*.

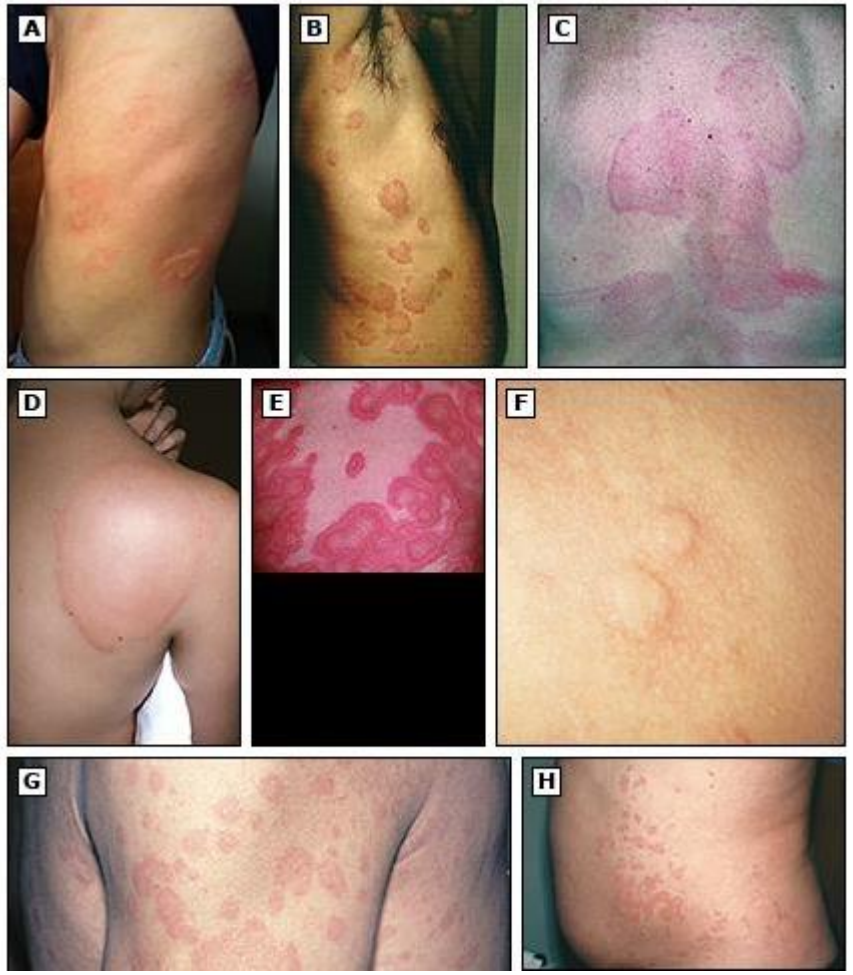
Urticaria

Inclusion Criteria	Exclusion Criteria
Pruritic	Fever
Blanching	Petechiae/purpura
Central swelling/ surrounding erythema	Blisters
Persists < 24 h	Severe joint pain



Clinical manifestations

- Urticarial lesions are **circumscribed, raised, erythematous plaques, often with central pallor.**
- Lesions may be round, oval, or serpiginous in shape and vary in size from less than 1 centimeter to several centimeters in diameter.

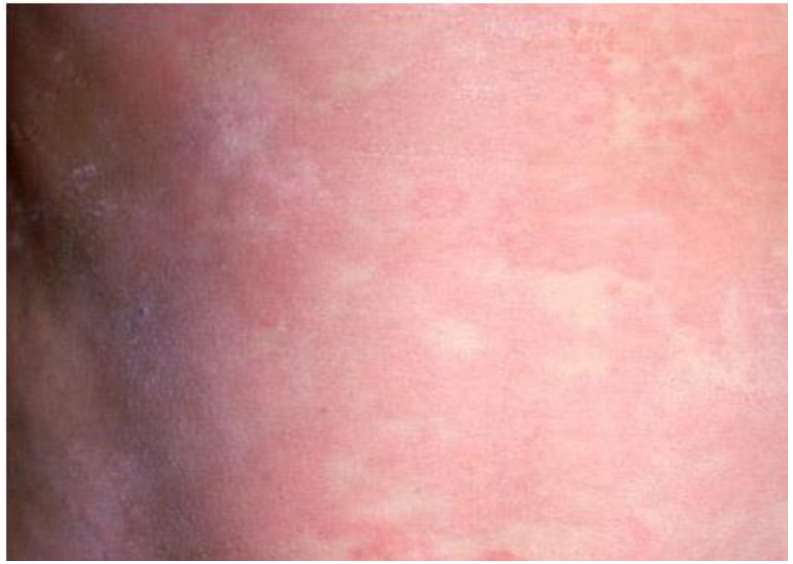


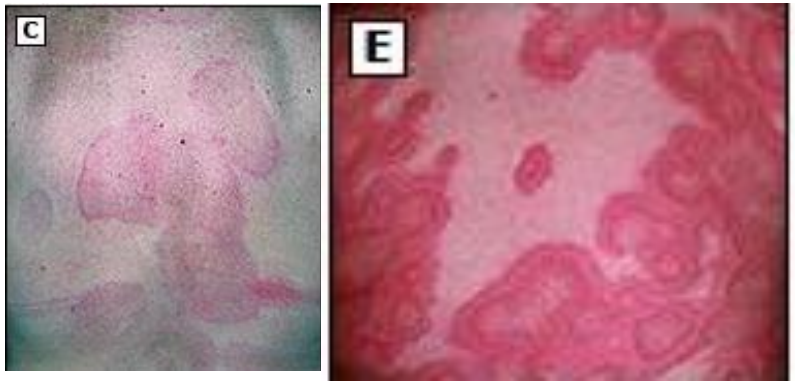
Clinical manifestations

- They are **intensely itchy.**
- Pruritus may **disrupt** work, school, or sleep.
- Symptoms often seem **most severe at night**.
- Individual lesions are **transient**, usually appearing and enlarging over the course of minutes to hours and then disappearing within 24 hours.

Clinical manifestations

- Lesions may coalesce as they enlarge.
- Urticarial lesions are **not normally painful** and resolve without leaving residual ecchymotic marks on the skin, unless there is trauma from scratching.
- If lesions are **long-lasting, painful, or leave residual bruising**, the diagnosis of urticarial vasculitis should be considered.





Clinical manifestations

- **Any area of the body**
- Areas in which **clothing compresses** the skin (eg, under waistbands) or skin **rubs together** (axillae) are sometimes affected more dramatically.
- Typically, compressed areas become more severely affected once the **restricting clothing has been removed.**

Angioedema

Swelling of the deep dermal & subcutaneous or submucosal tissues, usually affects the **face and lips, extremities, and/or genitals**.

May co-exist with urticaria

- 50% have both urticaria and angioedema
- 40% have urticaria alone
- 10% have angioedema alone
  - Bradykinin mediated (Hereditary angioedema, ACE inhibitor associated angioedema)
  - Idiopathic angioedema (histaminergic, non-histaminergic)

Urticaria: acute vs chronic

Acute

- Symptoms for <6 weeks
- More common in children and atopics

Chronic

- Symptoms continuously or intermittently (daily or almost daily) for ≥ 6 weeks
- More common in adults
- Female/male = 2:1
- No increased incidence in atopics

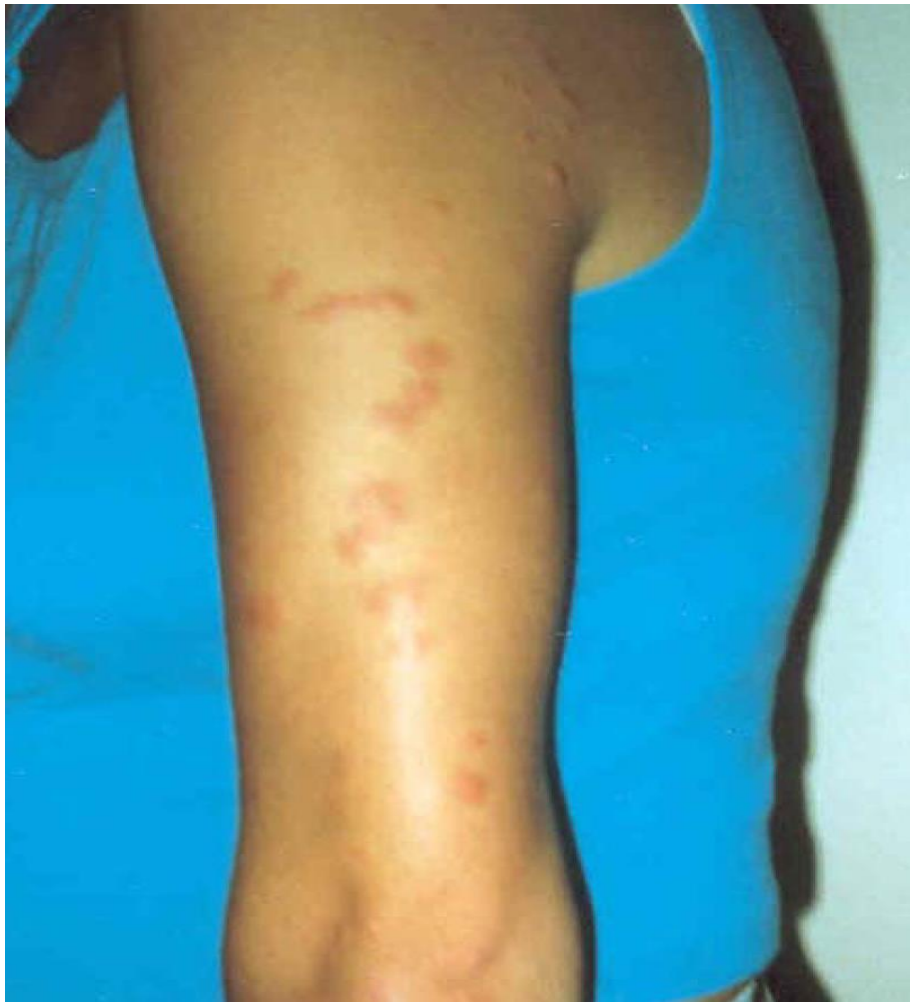
Causes of acute urticaria

- **IgE mediated** allergy (food, contact, medication, insect venom)
- Early **contact** dermatitis (poison ivy, nickel)
- Exacerbation of **Physical** urticaria (cold urticaria, cholinergic urticaria)
- **Non-IgE** medication (NSAIDs, opioid)
- **Papular** urticaria caused by insect sting (fleas, scabies, bed bugs)
- **Infection** (parvovirus B19, EBV, other viral)
- **Food toxin** (scromboid)

Identifiable causes of urticaria

Infections	Viral, Parasitic, Bacterial	
IgE-mediated allergic	Medications Insects Foods, Food additives Blood products	Latex (contact or inhaled) Contact allergens (animal saliva, raw foods) Aeroallergens (rare)
Direct mast cell activation	Narcotics/opiates Muscle relaxants (succinylcholine)	Radiocontrast agents Vancomycin
Physical stimuli	Dermatographism Delayed pressure Cold Cholinergic	Vibratory Aquagenic Solar Exertion/exercise
Miscellaneous	NSAIDs Serum sickness Transfusion (non IgE-med)	Hormone-associated (progesterone) Stinging nettle

Bedbugs bites resembling urticaria



Scarupa et al. J Allergy Clin Immunol 2006;117:1508-9

Common causes of chronic urticaria

- Autoimmune
- Physical urticaria (cold urticaria, cholinergic urticaria)

Epidemiology

Acute	Inducible (physical)	Chronic Spontaneous (CSU)
25% of people at some time in their lives		0.5 – 1% of people
80-90% respond to antihistamines, remaining 10% may need steroids	80-90% respond to antihistamine, except for pressure urticaria	45-50% respond to antihistamines
May be associated with angioedema	May be associated with angioedema	40-50% also have angioedema

Types of physical urticaria

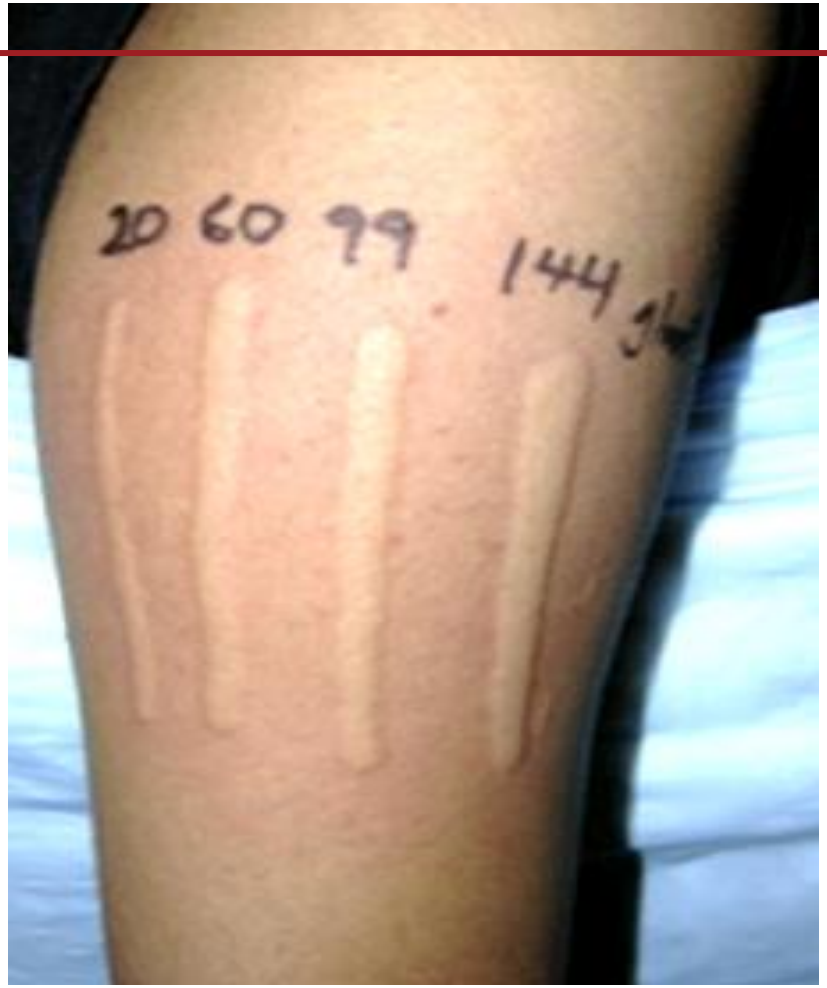
- Pressure
- Symptomatic dermatographism
- Cholinergic
- Acquired cold-induced
- Sun-induced

Dermatographism

Scratching induces linear urticaria

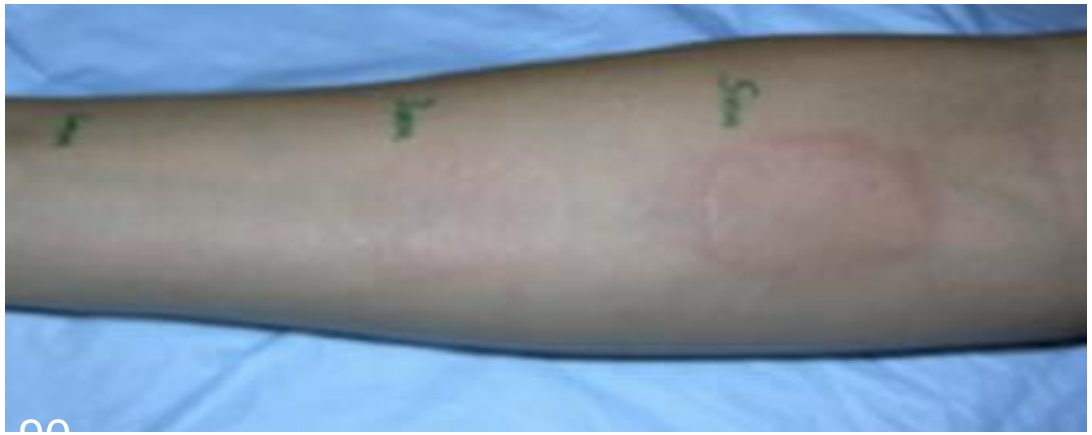
Short-lived - minutes

Responds to antihistamines



Acquired cold urticaria

- Diagnosis – ice cube test on forearm for 5 minutes, symptoms during re-warming
- Management – avoid cold, particularly swimming in cold water which can induce hypotension, antihistamines



Pathophysiology

- Urticaria is mediated by cutaneous mast cells in the superficial dermis.
- **Basophils** have also been identified in lesional biopsies.
- Mast cells and basophils release **multiple mediators** upon activation including histamine (which causes itching) and vasodilatory mediators (which cause localized swelling in the uppermost layers of the skin).
- The same process gives rise to angioedema when mast cells deeper in the dermis and subcutaneous tissues are activated.

Pathophysiology

- Principal cellular mediator is **histamine** in both acute & chronic spontaneous urticaria – mast cells (and basophils)

- 4-64% of patients have IgG antibodies to the high affinity IgE receptor which activates basophils and mast cells based on rates investigated by 14 studies

Kolkhir et al. J Allergy Clin Immunol 2017;139:1772-81.

Effect of urticaria on quality of life

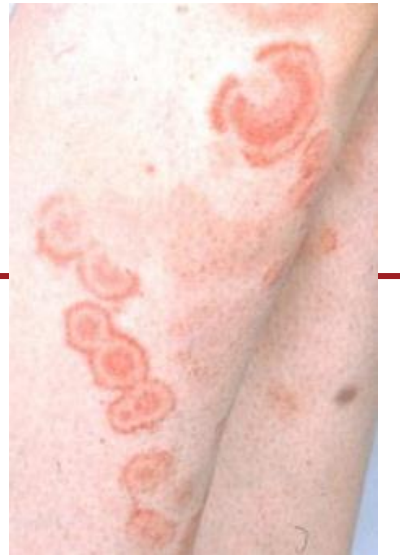
- Urticaria can have a significant detrimental effect on quality of life (QOL) due to **constant itch, effect on sleep and side-effects of medication**
- **Poor QOL / stress can be a trigger** for urticaria
- **Women tend to suffer more** than men
- Ensure that QOL/life stressors/events are assessed/discussed in patients with urticaria as this can **improve patient satisfaction/ outcome**

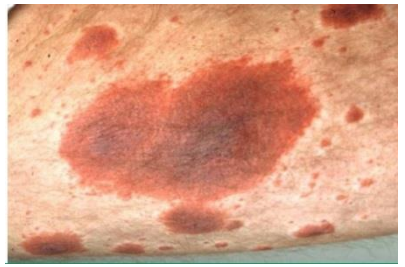
Urticaria activity score for chronic urticaria

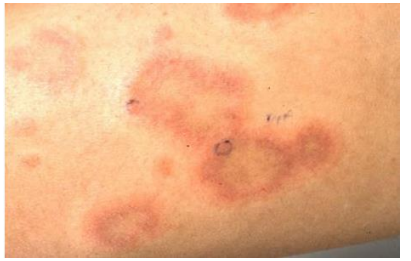
UAS7 Score	Wheals	Pruritus
0	None	None
1	Mild (<20/day)	Mild (not troublesome)
2	Moderate (20-50/day)	Moderate (troublesome, but sleeps okay)
3	Intense (>50/day or confluent)	Intense (interferes with daily life/sleep)

Systemic disorders that may include urticaria

Urticarial vasculitis





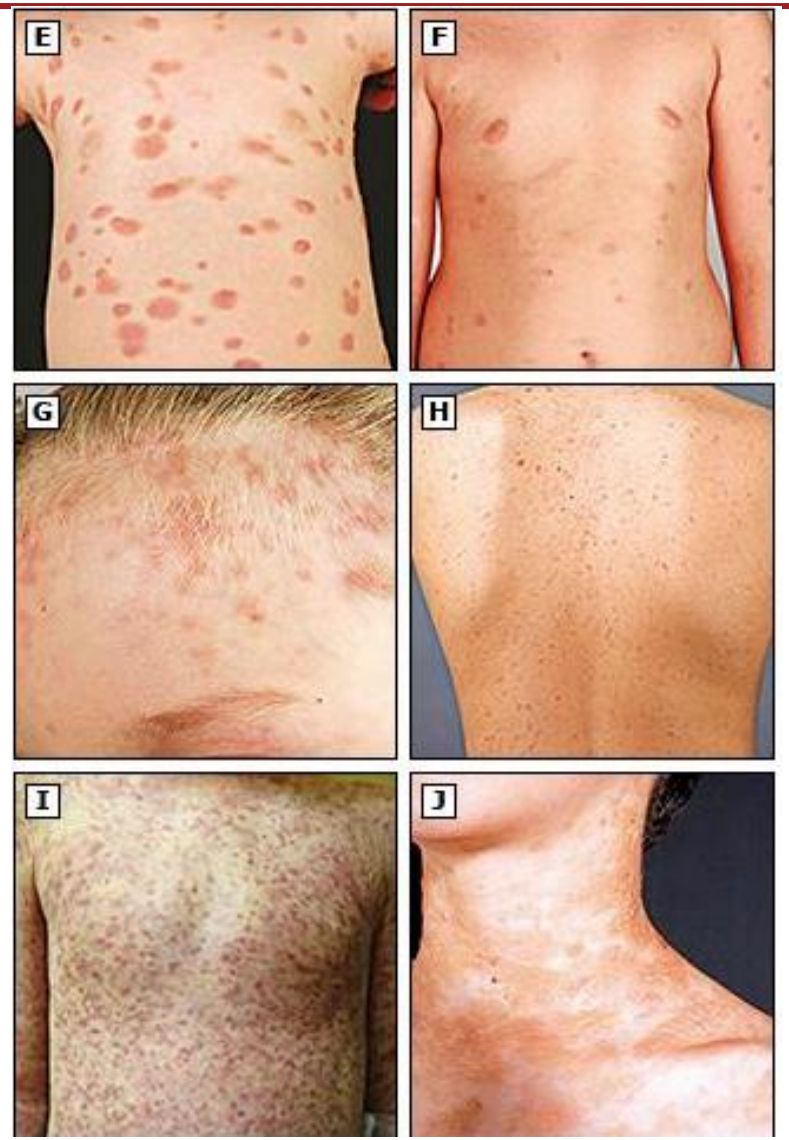


- individual lesions are
  - **painful**,
  - **long-lasting** (longer than 24 to 36 hours),
  - appear **purpuric or ecchymotic**, or leave residual ecchymosis or hyperpigmentation upon resolution (in the absence of trauma from scratching)
  - **fever, arthralgias**, arthritis, weight changes, bone pain, or lymphadenopathy.
  - may occur in the setting of another **rheumatologic** disorder or rarely, a **malignancy**

Mastocytosis and mast cell disorders

- patients present with apparent allergic reactions and anaphylaxis to a variety of triggers.

- Characteristic skin findings are helpful in diagnosis.



SLE, RA, Sjögren, celiac, autoimmune thyroid disease, other autoimmune diseases, small vessels vasculitis (Henoch)

- Urticaria may be a presenting manifestation or occur sporadically over time in patients with autoimmune conditions
- The etiology is unclear but may be due to **direct mast cell activation via complement receptors** or due to the generation of autoantibodies that may result in anaphylactoid degranulation.
- **Screening** for these disorders in the setting of an acute episode of urticaria is **not indicated**, unless there are other preceding symptoms that suggest that one of these disorders may be present.

Malignancies

- IgM and IgG paraproteinemias.
- Etiology? complement-mediated pathways.
- urticaria is persistent and becomes chronic.

Evaluation and diagnosis

- diagnosed **clinically**, based upon a detailed history and physical examination confirming the presence of characteristic skin lesions

Clinical history

- other signs and symptoms of a **generalized allergic reaction or anaphylaxis?**
  - chest tightness dyspnea, hoarse voice, throat tightness, nausea, vomiting, crampy abdominal pain, lightheadedness, and other symptoms
- hives **previously** in the past?
  - repeatedly with infections in children.
  - Following NSAID in adults
- **other** disorders?
  - symptoms or signs to suggest an underlying systemic disorder? unexplained fever, weight loss, arthralgias, arthritis, or bone pain

Clinical history

- review events in the hours before the urticaria appeared.
  - What had **ingested** (foods, beverages, candy)?
  - Was involved in **exercise or physical** exertion?
  - Was exposed to extremes of **temperature** or stung by an **insect**?
- any new **medications/supplements** in the preceding days or weeks
- recent **travel** (and symptoms of parasitic infection)
- A complete review of systems is valuable in the patient with new-onset urticaria.

Physical examination

- **directly visualizing** lesions in order to make the diagnosis with certainty, since the term "hives" is used nonspecifically by patients.
- If no lesions, **showing photographs**, asking if their lesions look similar.
- Individual urticarial lesions usually appear and resolve completely within 24 hours.
- If the patient is unsure of the duration of the lesions, **a lesion can be circled** with a pen and time to resolution noted.

Laboratory work-up

No diagnostic testing may be indicated

- routine laboratory testing in patients whose history and physical examination lack atypical features rarely yields clinically significant findings

Immediate hypersensitivity skin testing for inhalants or foods is not warranted

Skin biopsy may be performed when vasculitis is suspected (bruising, persistence >48 h)

Autoimmune associations of CSU

- Antibody to alpha subunit of the high affinity IgE receptor – 35-40%
- IgG antibody to IgE – 5-10%
- Anti-thyroid antibodies (anti thyroglobulin or anti peroxidase) – 25%
- Low titer ANA with speckled pattern (with no evidence of SLE) – 30%
- Clinical associations: increased incidence of Hashimoto’s

Laboratory studies

- typically **normal** in patients who **lack** any history or physical findings to suggest an underlying disease process or urticarial vasculitis
- For such patients presenting with new-onset urticaria (± angioedema), **laboratory testing is not indicated**
- In patients in whom **a specific etiology** is suspected, laboratory studies and further evaluation should be directed at establishing or excluding that cause.

Tests for allergic causes

- if the **clinical history** reveals a specific trigger to which the patient was exposed shortly before the onset of symptoms (within **one to two hours**).
- serum tests for allergen-specific immunoglobulin E (IgE) antibodies
- the interpretation of allergy tests can require some expertise.
- A **positive result is suggestive**, although not diagnostic, of allergy, and a **negative result does not exclude** allergy.
- Because of this, patients suspected of having an allergy **should be referred** to an allergist/immunologist for further evaluation when possible.
- **Skin tests** with fresh food, which should be performed by an allergy specialist, is probably the most convenient, inexpensive, and sensitive way to detect food hypersensitivity.

Skin biopsy

- not routinely needed for the diagnosis of CSU.
- a 3 mm punch biopsy of a newly formed lesion to exclude vasculitis in one or more of the following features:
- lesions that persist beyond 24 hours, painful rather than pruritic, accompanying petechial or purpuric characteristics, or leave residual pigmentation
- elevated CRP/ESR and/or systemic symptoms (arthralgias, fever).
- Symptoms unresponsive to appropriate doses of antihistamines

Differential diagnosis

Presence or absence of pruritus is a helpful

Nonpruritic conditions

- viral exanthems
  - erythema infectiosum (fifth disease), Epstein-Barr virus, enteroviruses, and measles.
  - not pruritic
  - erythematous maculopapular eruptions that persist for days.
  - Fever
  - macules are relatively fixed

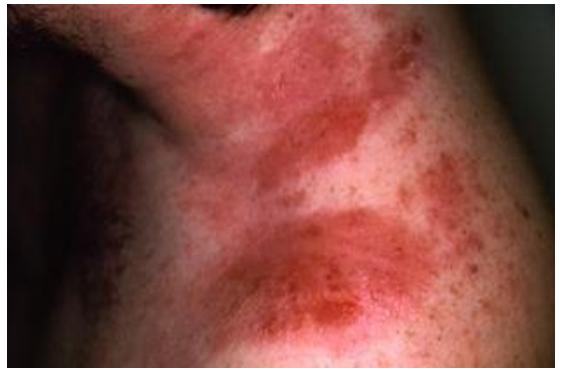
Nonpruritic conditions

- **Auriculotemporal syndrome**: nonpruritic flushing and/or sweating of the skin over the cheeks or jawline) transiently after eating following damage to the nerve secondary to forceps delivery, viral infection, surgery, or other local trauma.

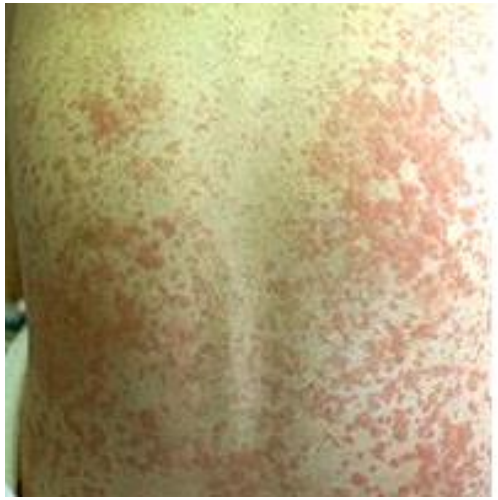
- **Sweet syndrome**: recurrent episodes of painful, long-lasting inflammatory papules and plaques associated with fever, arthralgias, and peripheral leukocytosis.

Pruritic conditions

- **Atopic dermatitis**: intensely pruritic erythematous patches with papules and some scaling.



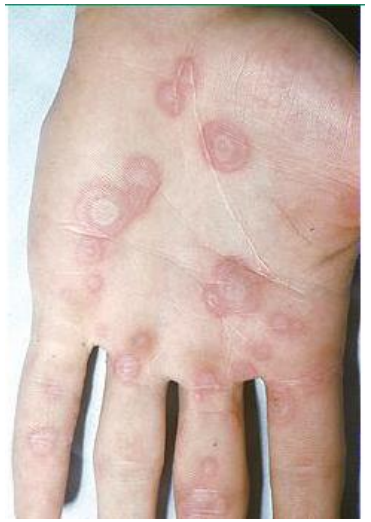
- **Contact dermatitis**: erythematous, papular dermatitis, often with areas of vesiculation, distributed in the areas of direct contact.



- **Drug eruptions**: morbilliform or exanthematous small macules and/or papules
- **Insect bites**

Pruritic conditions

- **Bullous pemphigoid**: start with pruritus, ±urticaria, then blistering
- **Erythema multiforme minor**: erythematous, iris-shaped macules and vesiculobullous lesions with a target appearance, may be painful or pruritic and distributed symmetrically on the extensor surfaces of the extremities (particularly the palms and soles). **Individual lesions last several days, unlike urticaria.**



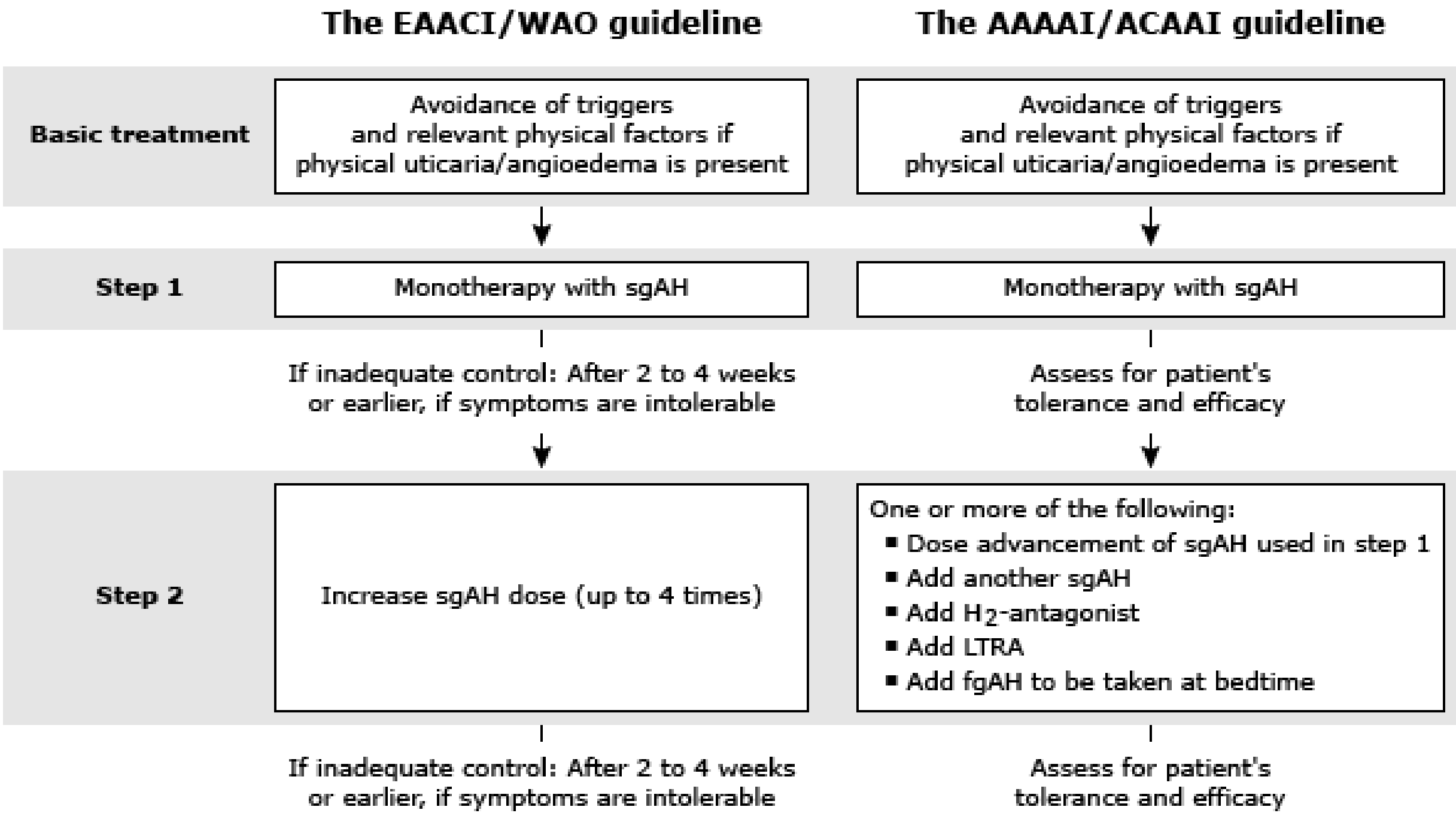
- **Plant-induced reactions** – Poison ivy and poison oak can present with urticaria-like lesions initially that evolve into vesicular lesions.

Treatment options for urticaria/angioedema

- In case of only angioedema consider HAE and refer to a specialist – risk of upper airway obstruction which will **not respond to IM epinephrine**!
- In vasculitis and refer for biopsy and treatment with immunosuppressives

Treatment

- Approximately two-thirds of cases of new-onset urticaria will be self-limited and resolve spontaneously.


The EAACI/WAO guideline
The AAAAI/ACAAI guideline
Basic treatment
Avoidance of triggers and relevant physical factors if physical uticaria/angioedema is present
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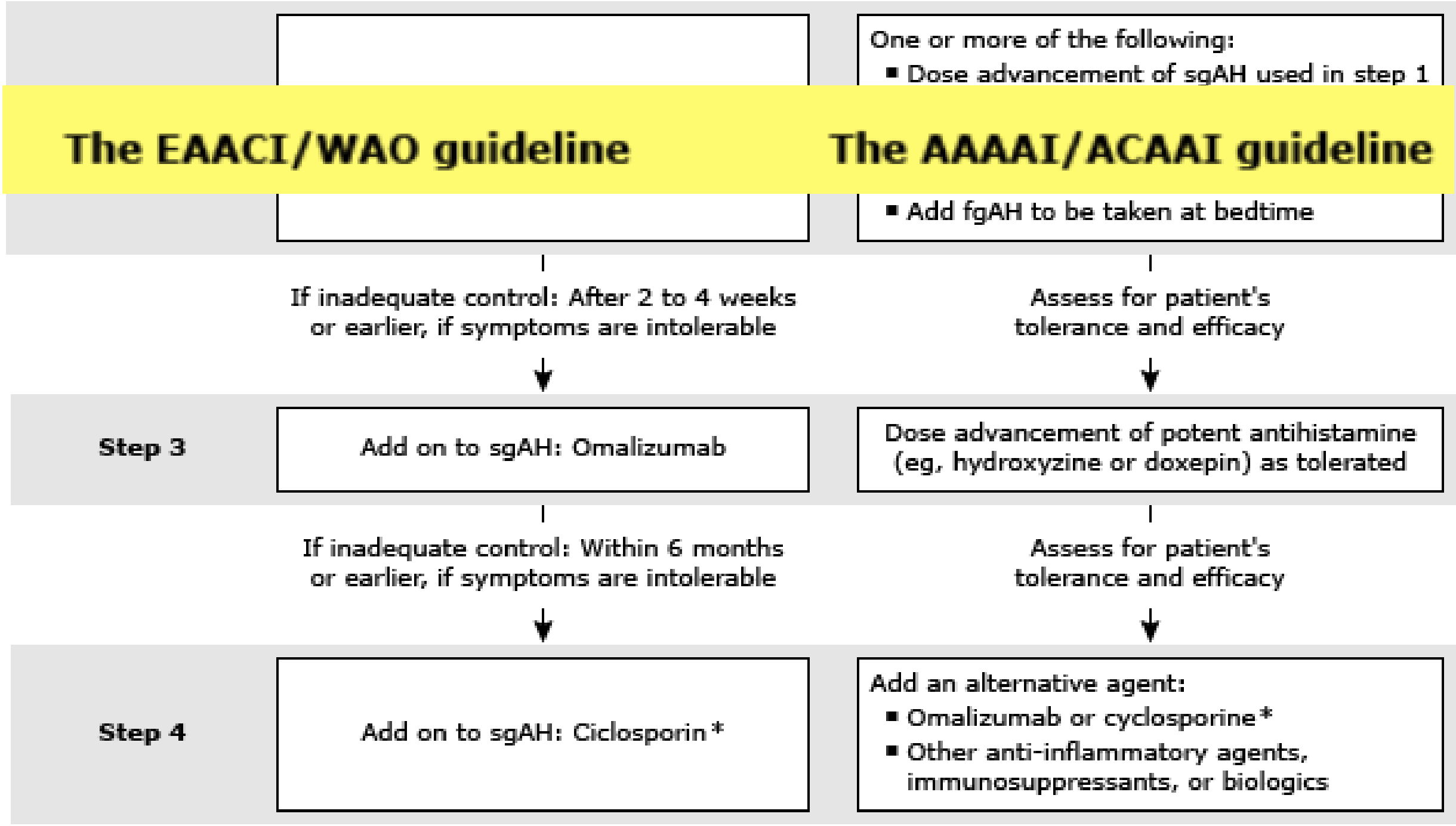
Step 1
Monotherapy with sgAH
Monotherapy with sgAH
If inadequate control: After 2 to 4 weeks or earlier, if symptoms are intolerable
Assess for patient's tolerance and efficacy
Step 2
Increase sgAH dose (up to 4 times)
One or more of the following:
Dose advancement of sgAH used in step 1
Add another sgAH
Add H2-antagonist
Add LTRA
Add fgAH to be taken at bedtime
If inadequate control: After 2 to 4 weeks or earlier, if symptoms are intolerable
Assess for patient's tolerance and efficacy


The EAACI/WAO guideline
The AAAAI/ACAAI guideline
One or more of the following:
Dose advancement of sgAH used in step 1
Add fgAH to be taken at bedtime
If inadequate control: After 2 to 4 weeks or earlier, if symptoms are intolerable
Assess for patient's tolerance and efficacy
Step 3
Add on to sgAH: Omalizumab
Dose advancement of potent antihistamine (eg, hydroxyzine or doxepin) as tolerated
If inadequate control: Within 6 months or earlier, if symptoms are intolerable
Assess for patient's tolerance and efficacy
Step 4
Add on to sgAH: Ciclosporin*
Add an alternative agent:
Omalizumab or cyclosporine*
Other anti-inflammatory agents, immunosuppressants, or biologics

Management of chronic urticaria

Step 4
(inadequate response after 4-6 months)

Add or switch to Cyclosporine
Add Omalizumab or cyclosporine or other anti-inflammatory agents

Step 3
(inadequate response after 2-4 weeks)

Add Omalizumab
Dose advancement of potent antihistamine (Hydroxyzine, Doxepine) as tolerated

Step 2
(inadequate response after 2-4 weeks)

≥one:
Increase non-sedating H1 Antihistamine
Add another non-sedating H1 antagonist
Add H2 antagonist
Add leukotriene receptor antagonist
Add bedtime sedating H1 antagonist

Step 1

Non-sedating H1 Antihistamine monotherapy

Basic treatment

Avoiding of triggers, physical factors

Pregnant and lactating women

- may be treated initially with loratadine (10 mg once daily) or cetirizine (10 mg once daily). T
- The first-generation agent chlorpheniramine, 4 mg orally every four to six hours, may also be safely used in pregnancy
- Lactating women may be treated with either cetirizine or loratadine (both are dosed at 10 mg once daily), which are minimally excreted in breast milk and should not cause sedation or poor feeding in the infant.


Thank you