Chronic Urticaria
Management

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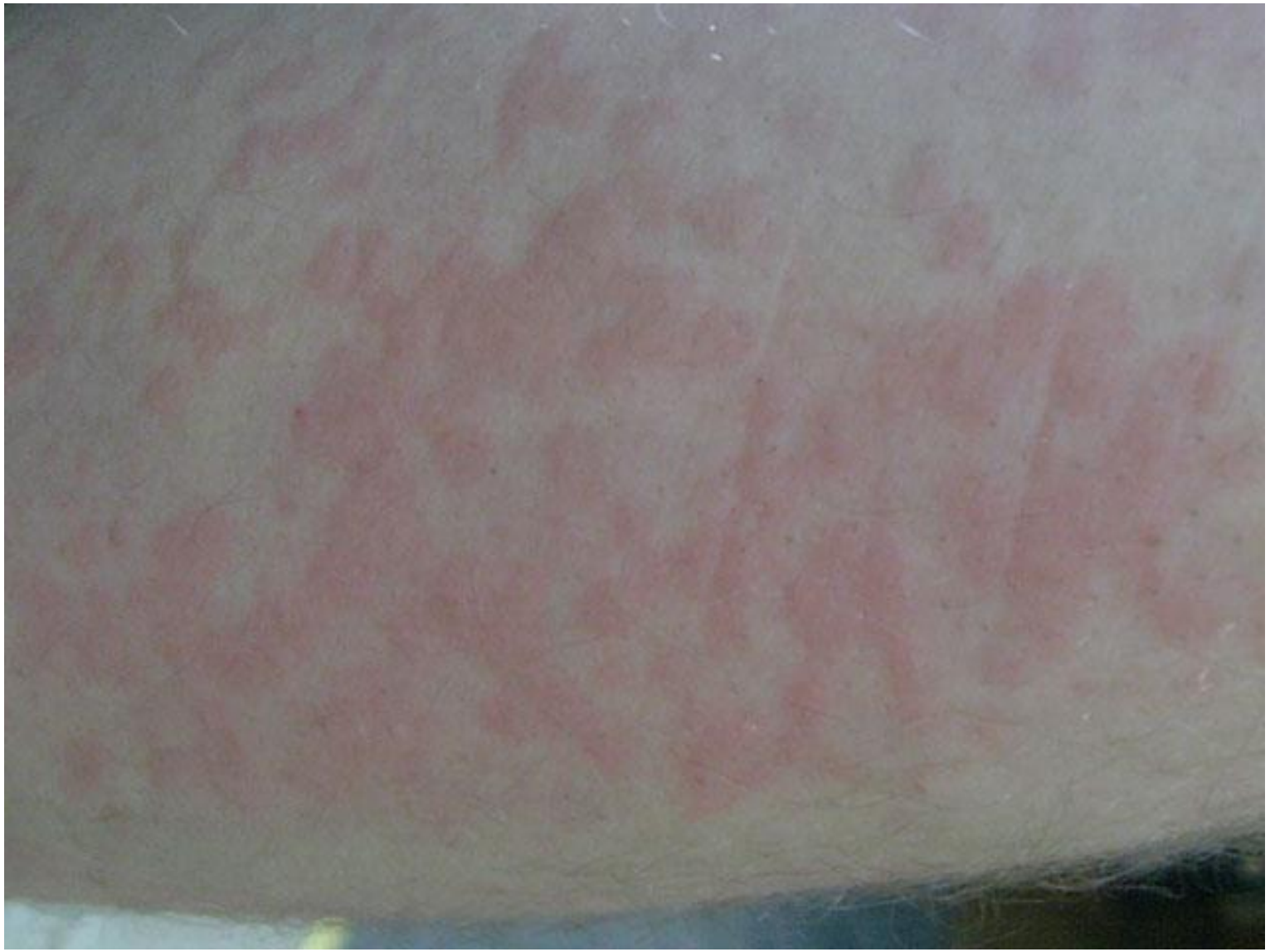

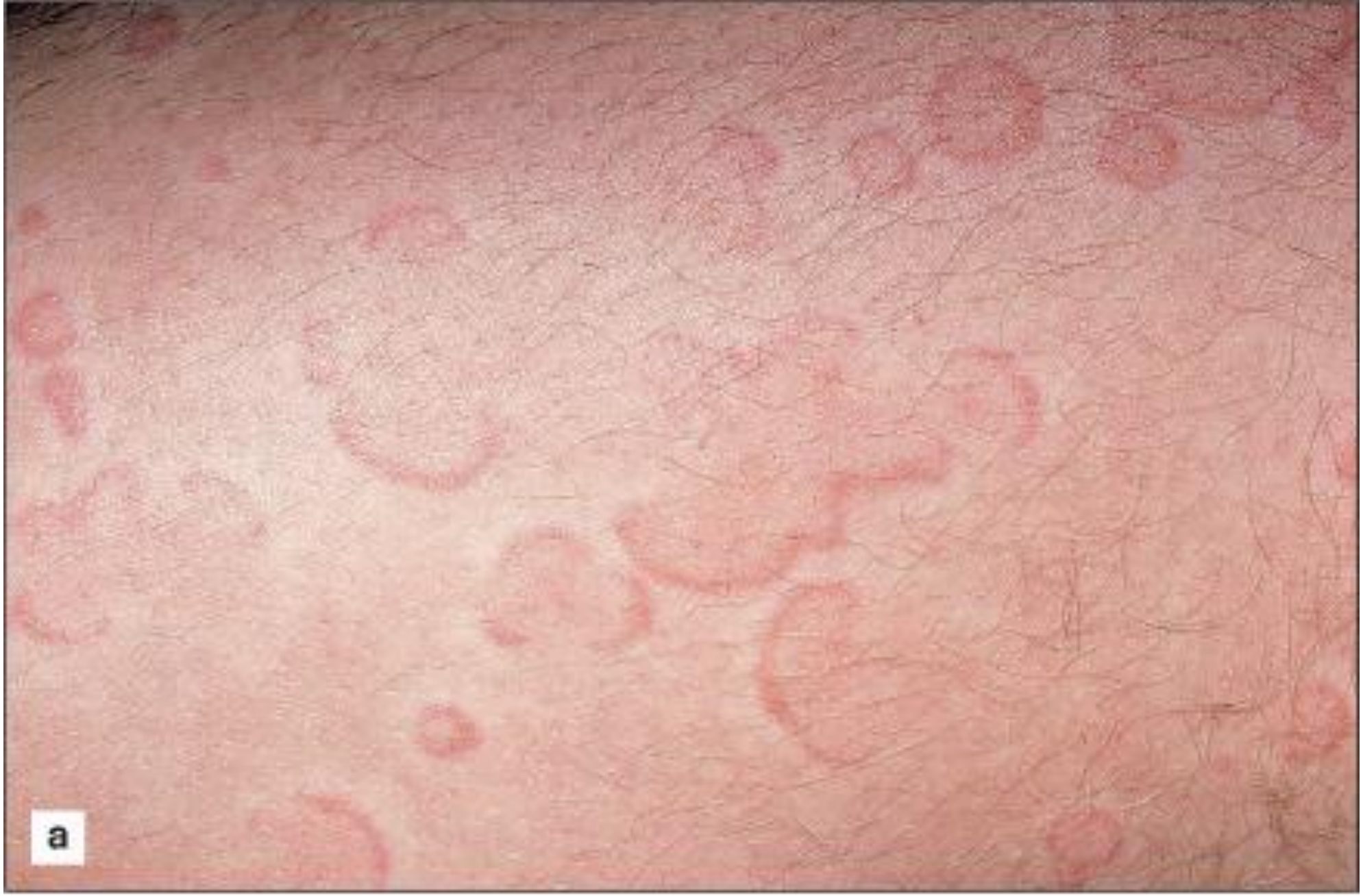

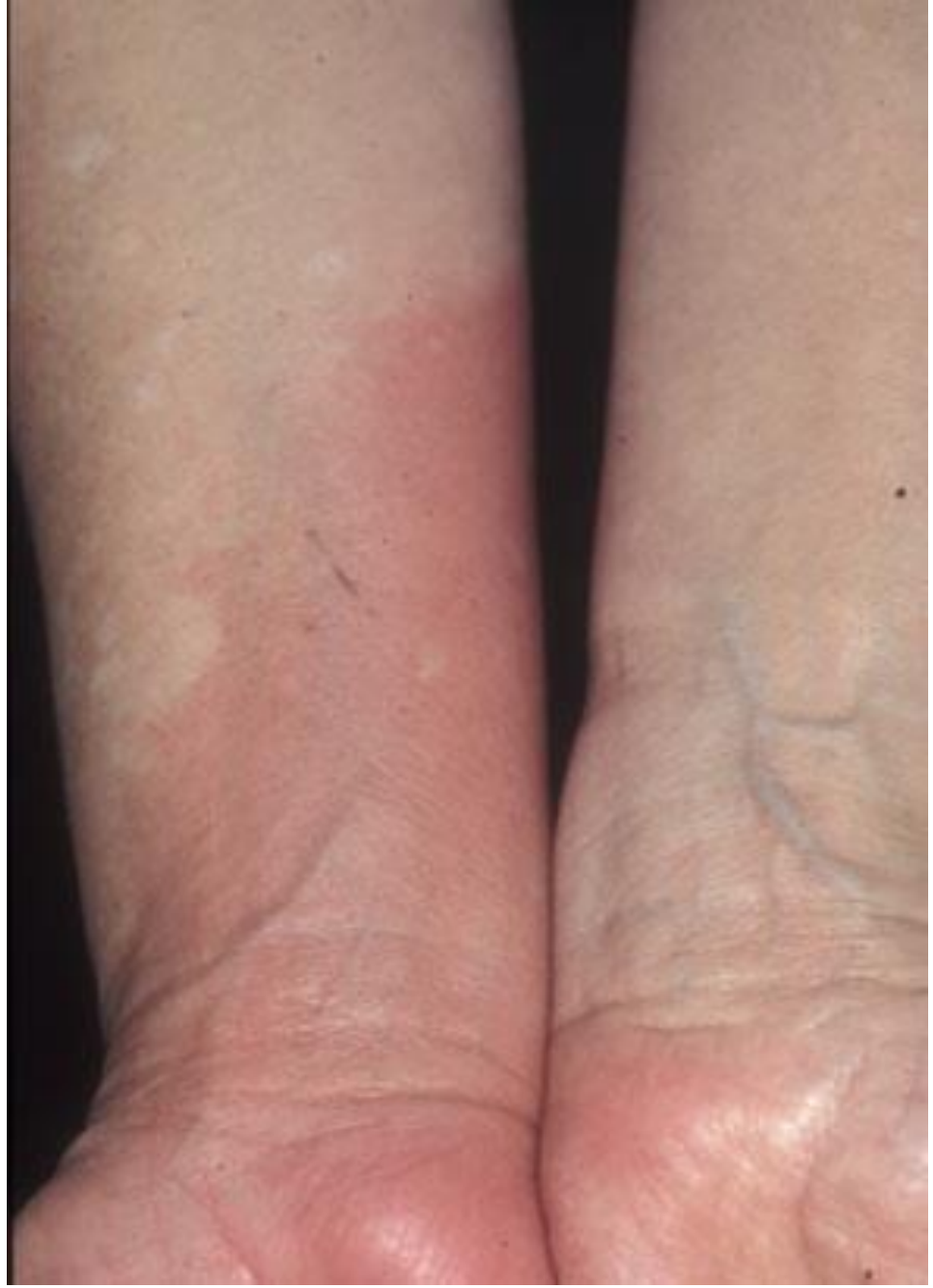

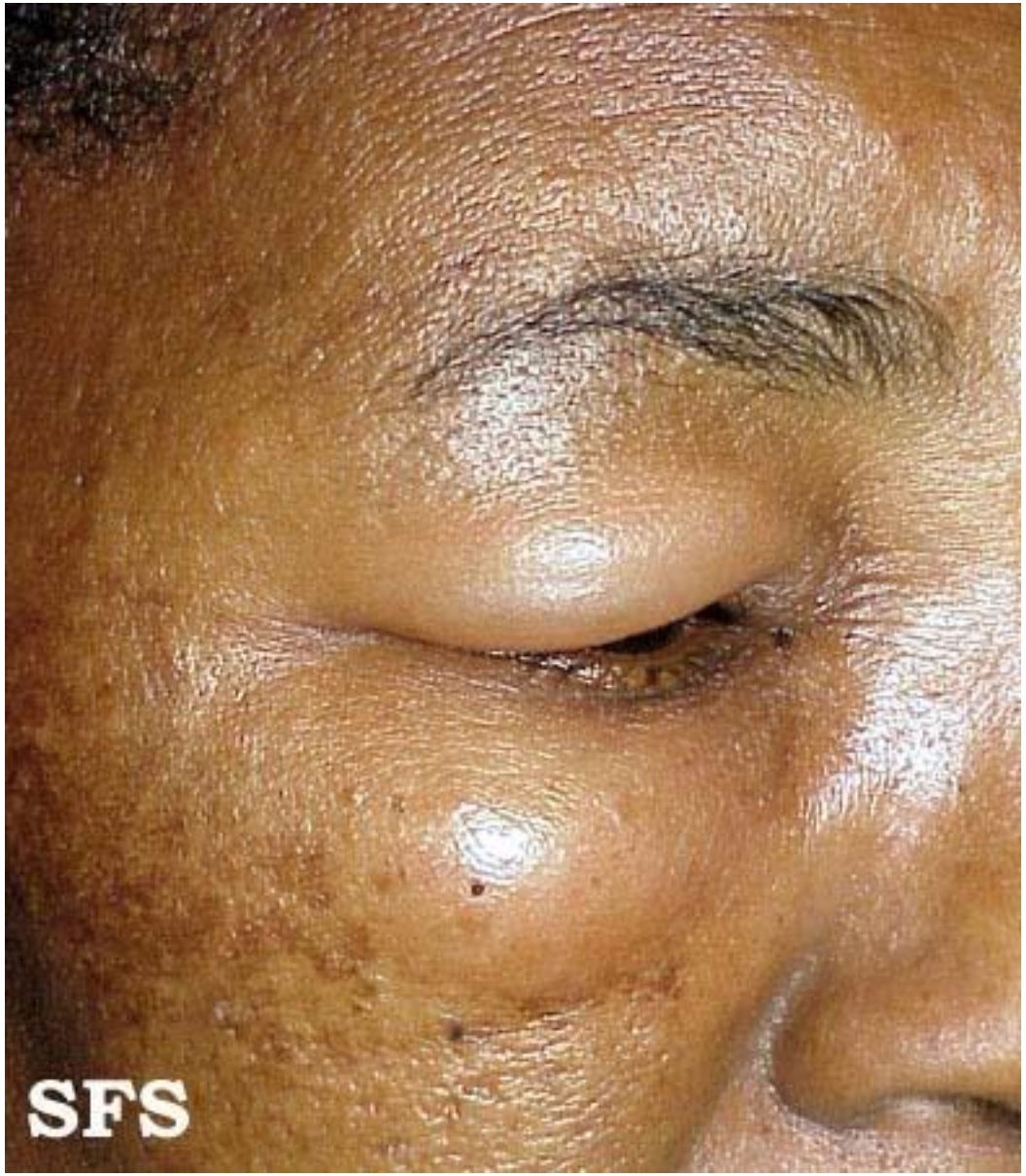
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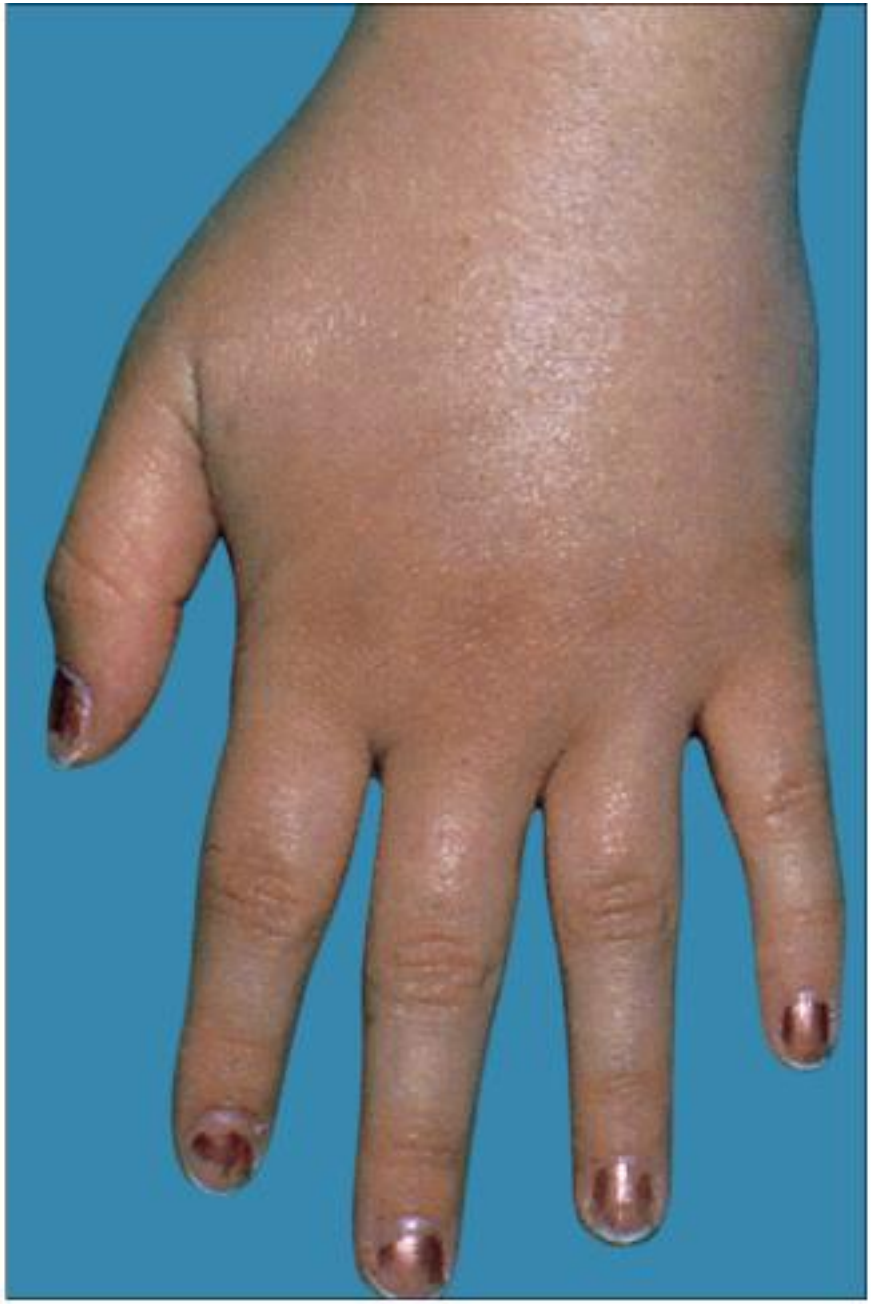
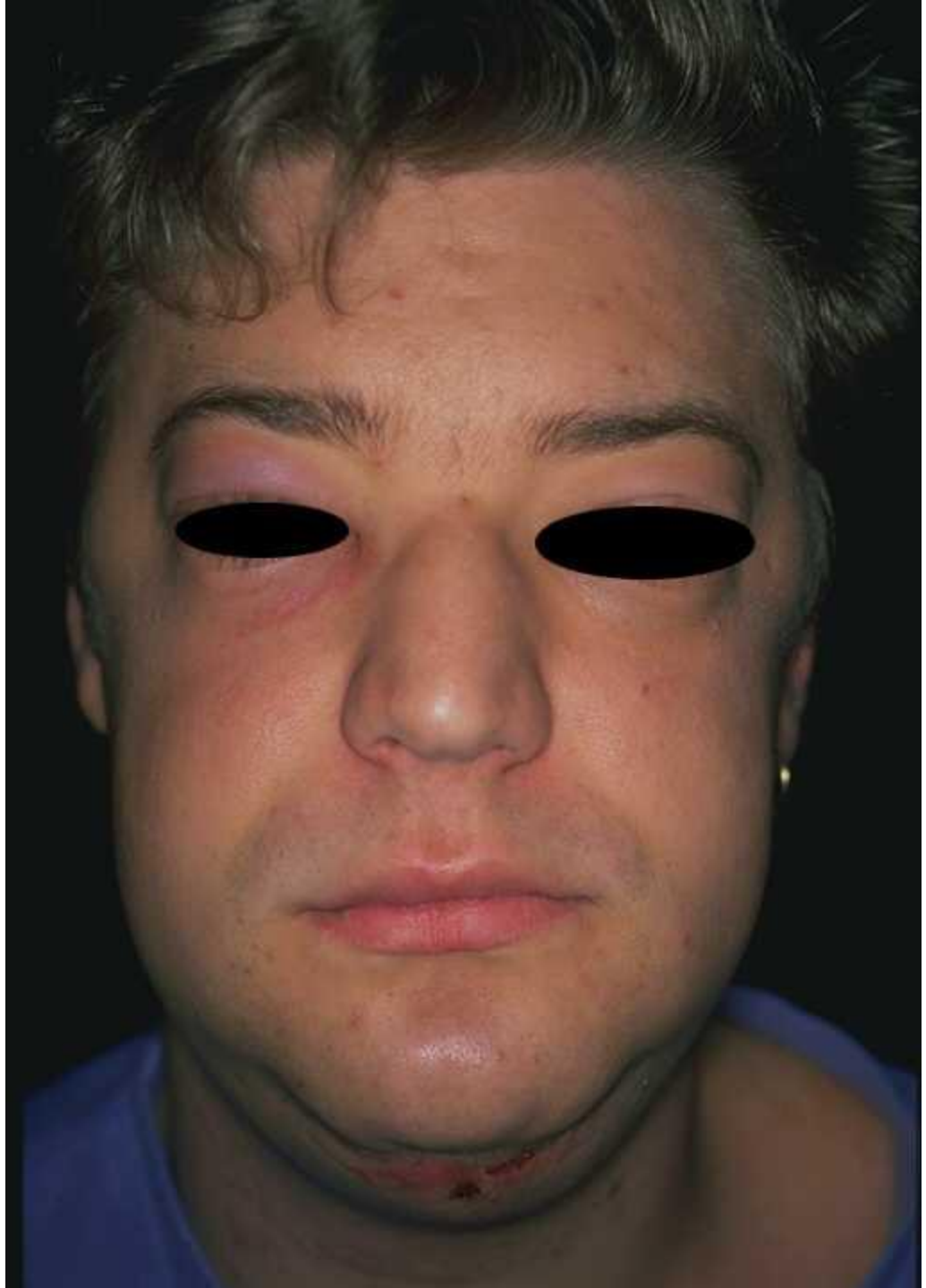
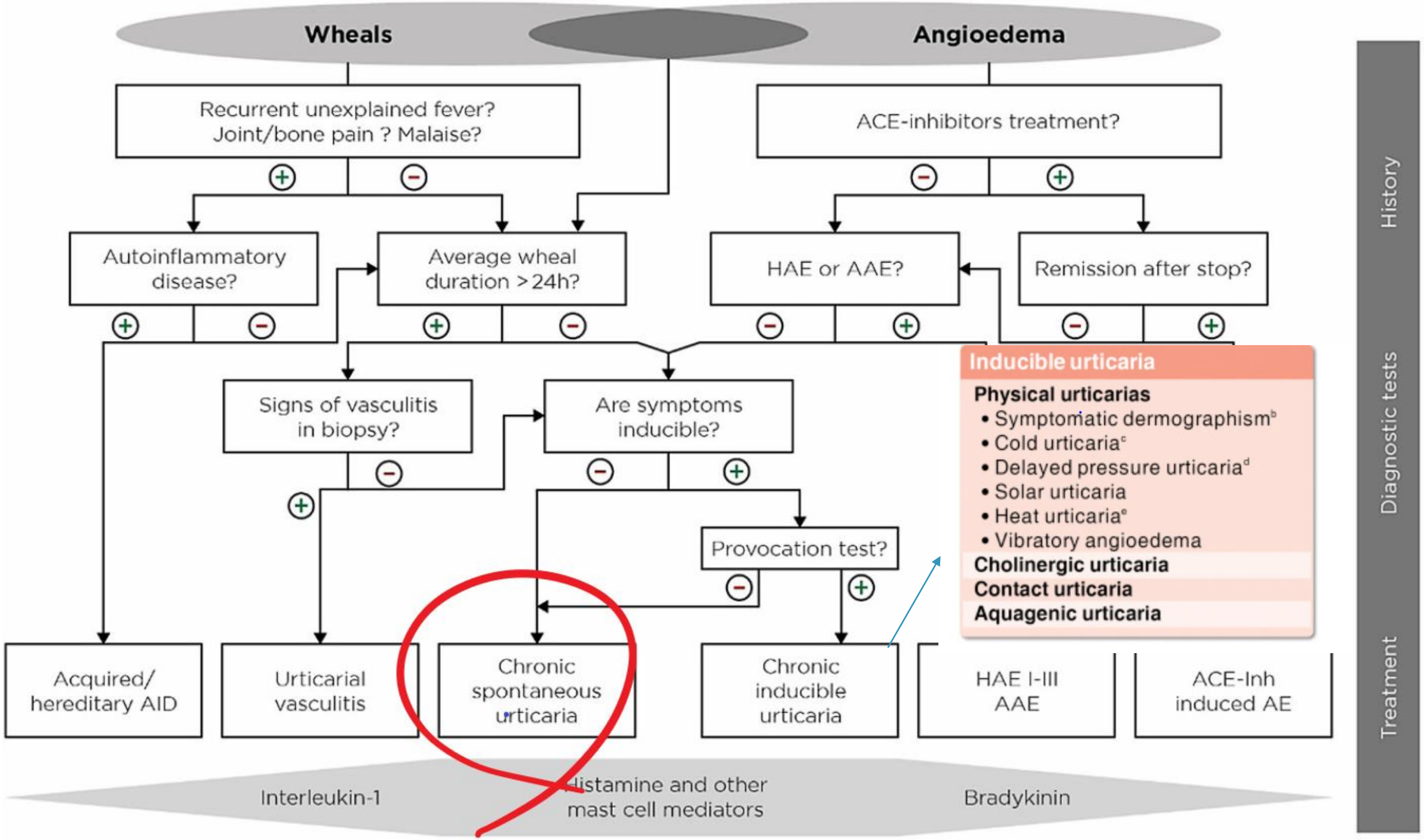




Introduction

- recurrent urticaria , angioedema, or both, for a period of six weeks or longer
- self-limited disorder in most patients
- average duration of disease of two to five years
- The term "spontaneous" is included to differentiate CSU from several forms of physical urticaria
  - urticaria-predominant phenotype in approximately one-half of patients
  - a mixture of urticaria and angioedema in about 40 percent
  - mainly angioedema in 10 percent.
    - angioedema rarely lead to swelling of the tongue


Wheals
Angioedema
Recurrent unexplained fever? Joint/bone pain ? Malaise?
ACE-inhibitors treatment?
Autoinflammatory disease?
Average wheal duration >24h?
HAE or AAE?
Remission after stop?
Signs of vasculitis in biopsy?
Are symptoms inducible?
Provocation test?
Inducible urticaria
Physical urticarias
• Symptomatic dermographism[b]
• Cold urticaria[c]
• Delayed pressure urticaria[d]
• Solar urticaria
• Heat urticaria[e]
• Vibratory angioedema
Cholinergic urticaria
Contact urticaria
Aquagenic urticaria
Acquired/ hereditary AID
Urticarial vasculitis
Chronic spontaneous urticaria
Chronic inducible urticaria
HAE I-III AAE
ACE-Inh induced AE
Interleukin-1
Histamine and other mast cell mediators
Bradykinin
History
Diagnostic tests
Treatment

Epidemiology

- Both children and adults
  - more common in adults
- Women are affected twice as often as men
- begins in the third to fifth decades

Associated conditions

- With systemic symptoms: This subgroup had more severe and longer-lasting disease
- Atopic disorders
- Autoimmune disorders: in the decade after the onset of CSU
  - thyroid disorders
    - even in the absence of hypo- or hyperthyroidism, patients with thyroid autoantibodies are often poorly responsive to standard therapies for CSU and have more persistent disease
  - celiac disease
  - Sjögren syndrome
  - systemic lupus erythematosus
  - rheumatoid arthritis
  - type 1 diabetes mellitus
  - Antinuclear antibodies: more prevalent
- Malignancy: controversial

Evaluation and Diagnosis

- History
  - drugs, travel, infections, changes in health status, other atopic conditions
  - fever, weight loss, arthralgias, arthritis, cold or heat sensitivity, abdominal pain, and bone pain
- Aggravating factors
  - Physical factors –heat (hot showers, extreme humidity) , tight clothing or straps can also aggravate symptoms.
    - In contrast, patients in whom physical factors are the **main** trigger for symptoms are more appropriately diagnosed as having a physical urticarial syndrome,
  - Anti-inflammatory medications
  - Stress
  - Variations in dietary habits and alcohol

Evaluation and Diagnosis

A complete blood count with differential: usually normal

- Eosinopenia (an absolute eosinophil count of <50 cells/microL) :severe disease, autoimmunity, and poor response to treatment with second generation antihistamines and omalizumab
  - glucocorticoids, cause a rapid reduction in eosinophil counts.
- Eosinophilia :atopic disorder or parasitic infection
- Basopenia :more severe disease

CRP or ESR –normal

- Significant elevations :severe disease, quality of life impairment, and non-response to antihistamines
- Further investigation for systemic diseases: antinuclear antibodies, cryoglobulins, hepatitis B and C serologies, total hemolytic complement, and a serum protein electrophoresis

TSH level –in adults and also thyroid autoantibodies (antithyroglobulin, antimicrosomal antibodies, or both)

- *Helicobacter pylori*

Evaluation and Diagnosis

- **Skin biopsy :** not routinely needed for the diagnosis
- persist beyond 24 hours, are painful rather than pruritic, have accompanying petechial or purpuric characteristics, or leave residual pigmentation
- An elevated CRP/ESR and/or systemic symptoms
- Symptoms that are unresponsive to appropriate doses of antihistamines
- features suggestive of mastocytosis

Prognosis

- spontaneous remission at one year of approximately 30 to 50 percent
- Remission rates in children : higher
- persist beyond five years in up to 30 percent of patients
- A longer duration of symptoms
  - more severe disease
  - the presence of angioedema
  - thyroid autoimmunity
  - Hypertension : regardless of medicine
  - eosinopenia and basopenia
- Patient education :rarely a sign of another underlying disease, rarely permanent, rarely puts the patient at any acute risk

Goal of therapy

- educe or eliminate symptoms for as long as the condition lasts
- The majority of available therapies have not been shown to cure CSU or impact how long the underlying disorder persists

Stepwise approach to treatment

- **Step 1**
- a second-generation antihistamine at standard therapeutic dose
  - Cetirizine, 10 mg once daily
  - Levocetirizine, 5 mg once daily
  - Fexofenadine, 180 mg once daily
  - Loratadine, 10 mg once daily
  - Desloratadine, 5 mg once daily

efficacy of H1 antihistamines in this disorder involve regularly dosed antihistamines

Stepwise approach to treatment

Step 2 :

- step 1 does not control symptoms adequately within one to two weeks

1. **Increase the dose of the second-generation antihistamine** :preferred by 2018 international guidelines
   - up to four times standard doses with desloratadine or levocetirizine 2–0–2
     - Not effective for all antihistamines
   - combining two different second-generation antihistamines when up-dosing American guidelines
2. **Add a different second-generation antihistamine**
3. **Add an H2 antihistamine** American guidelines

Stepwise approach to treatment

Step 2

4. **Add a leukotriene-receptor antagonist** not in 2018 international guidelines
   - allow at least four weeks to assess the impact
   - not lead to any significant improvement.

5. **Add a first-generation H1 antihistamine at bedtime** American guideline
   - Hydroxyzine
     - 10 to 25 mg. In children up to 12 years of age : 0.5 mg/kg. For children >12 years of age, 10 mg can be given initially.
   - Doxepin
     - 10 or 25 mg given at bedtime. Avoided in children <12 years of age
   - Cyproheptadine
     - children, 2 mg for children six years of age and younger, 4 mg for older children, and increasing to 8 mg

Stepwise approach to treatment

Step 3

- the dose of the first-generation H1 antihistamine may be advanced gradually American practice
- discontinue any medications that were added in step 2 that did not appear to benefit
- tolerance to performance impairment after three to five days of therapy

Hydroxyzine : increased in weekly increments
- 100 to 200 mg, divided into three or four doses
- children <6 years of age is 12.5 mg; 6 to 12 years of age: 25 mg; >12 years of age: 100 mg.

Doxepin –increased in weekly increments
- 100 to 150 mg, given once at bedtime or in divided doses
- Cardiotoxic
- obtain a baseline electrocardiogramdoses : chronic use of greater than 50 mg daily

International guidelines do **not** advocate the use of sedating antihistamines, unless there are no other options

avoids in children under 2y and older adults

Stepwise approach to treatment

- first- and second-generation H1 antihistamines reduce the major symptoms
- nonsedating antihistamines improve quality of life for patients, better tolerated
- a trial of H2 antihistamines can be considered as additive therapy in patients whose symptoms do not respond adequately to H1 antihistamines alone, but if no improvement is noted within two to four weeks, other therapies should be considered
- data in support of leukotriene modifiers are relatively weak

Stepwise approach to treatment

Step 4= refractory

- One months to several weeks (international guideline) to fully assess effectiveness
- antihistamines and other standard agents that were clearly helpful are continued
- Therapy is generally continued for a period of several months once control of symptoms has been achieved

1. Omalizumab
2. immunosuppressant : calcineurin inhibitors and mycophenolate mofetil
3. Anti-inflammatory : dapsone, sulfasalazine, and hydroxychloroquine

Omalizumab

- monoclonal antibody directed against IgE :preferred, > 12y (off-label<6y)
  - proven efficacy and also safety
  - high cost
  - No specific laboratories are required
  - omalizumab can reduce virus-mediated exacerbation(COVID-19)
- better response : higher baseline serum IgE levels
- not have a long-term disease-modifying effect, relapse when tapered or discontinued
- 300 mg injected subcutaneously every four weeks
- continue nonsedating H1 antihistamines initially and then taper as tolerated
- Benefit was frequently seen in the first month, and a majority of patients responded within four months (three doses)

Omalizumab

- 6 months at least
- history of refractory CSU for many years (eg, ≥3 years) :treat for a minimum of one year before considering tapering.

1. **complete resolution of symptoms and no breakthrough symptoms for two to three months**,
   - Lower dose (to 150 mg), and the interval between injections can be gradually lengthened.
     - no symptoms for a period of time on 150 mg every eight weeks, therapy can be stopped.
   - prolong the interval by one week per cycle
     - discontinue therapy if the patient's disease remains controlled with eight-week intervals
2. **partial responses to omalizumab at 300 mg**
   - higher doses (450 or 600 mg every four weeks) or more frequent doses (eg, 150 mg every two weeks)
   - Evaluate after three doses.
3. **minimal or inadequate control of symptoms :**discontinue after a four-month trial
4. **subsequent recurrence** :respond to omalizumab again

Omalizumab

- Most anaphylaxis occurred within 2h of injection during the first three applications
- no association between omalizumab and an increased risk of malignancy
- pausing omalizumab in the case of febrile infections or systemic need for treatment with antibiotics
- no contraindication to live vaccines: at least one week interval

Cyclosporine

- Patients who are positive for autoimmune antibodies
- rapid onset, degree of efficacy comparable with prednisone, lasting remission
- 3-4 mg per kg, divided into two doses. For most adults, this is 100 to 150 mg twice daily
- respond within one week or two, therapeutic response within four to eight weeks
- treat at a dose required for complete or near-complete control for three months
- taper the dose over several months, as tolerated.
- In the majority of patients, six to nine months

some require long-term therapy (two or three years) at the lowest effective dose

low-dose cyclosporine is associated with a significant improvement in clinical symptoms and relatively low risk of adverse events

Mycophenolate

- fewer adverse effects, works more gradually
- Start at 1000 mg twice daily and may be increased by 500 mg twice daily at monthly intervals if needed, up to a maximal dose of 2000 mg twice daily.
- If no improvement after one month of 2000 mg twice daily, discontinue it.
- 12-14 w of treatment
- 4-6 months of remission

Sulfones (Dapsone)

- Neutrophil on biopsy?????
- start with a dose of 100 mg daily.
- A 10 to 20 percent decline in hemoglobin (1 to 2 grams/dL) or hematocrit is common
  - do not stop therapy unless the decrease exceeds 25 percent.
- A four-week trial to determine effectiveness.
- taper antihistamine first, and then the dapsone is reduced over a period of several months
- Rapid onset, sustained remission

Hydroxychloroquine

- safety and low cost
- slow onset of action, in combination with dapsone or sulfasalazine
- No lasting remission
- start with a dose of 200 mg twice per day.
- A three-month trial to determine effectiveness.

Systemic glucocorticoids

- periodically to gain temporary control of symptoms during severe exacerbations
- at any point in therapy
- 20-50 mg initially
- five to seven days (max 10 d), followed by tapering by 5 mg every two to three days

addition of glucocorticoids to antihistamines during the initial weeks of treatment did not hasten the time required to achieve control of symptoms

Other therapies

Vitamin D

- the clinical significance of vitamin D supplementation remains unclear, although it may be an option for patients who wish to minimize other medications
- Sleep quality and pruritus scores improved in the high-dose (4000 international units daily)group

Dietary modification

- We do **not** routinely advise CSU patients to modify their diets
- if a patient is very motivated to try these diets, we do not object.
- aromatic compounds in certain foods such as many fruits and vegetables, seafood, and artificial preservatives
- trial of a minimum of two to three weeks is required

Other therapies

- **Phototherapy**
  - PUVA < NBUVB
- **Tumor necrosis factor (TNF)-inhibitors**
  - patients failed omalizumab, calcineurin inhibitors, anti-inflammatory agents
- **Methotrexate**
  - 5 to 25 mg/week. Effects observed after four weeks of therapy.
  - Negative studies also exist
- Colchicine
- Cyclophosphamide
- anticoagulants and antifibrinolytic agents
- Sirolimus
- Immune globulin

Maintenance therapy

- three months of good control prior to tapering therapies
  - reduce antihistamine doses every two to four weeks, beginning with first-generation agents
- If symptoms were easily and completely controlled with one or two agents may begin to taper therapy after one or two months of well controlled symptoms
- further than three months if:
  - Symptoms that were present for years, were very severe, were difficult to control
  - Concomitant physical urticarias, which tend to be longer-lasting than simple CSU
  - Symptoms that are mostly controlled but still present at a low level

Discontinue

- At any point in therapy, if an agent is ineffective, including completely antihistamine-resistant patients
- In patients dependent upon systemic glucocorticoids, we reduce the dose as quickly as possible

Special population

Pregnancy

- the least amount of medication possible
- second-generation H1 antihistamines alone, with occasional short courses of oral glucocorticoids
- Twofold higher doses of single agents or two separate antihistamine
- Omalizumab has been used safely for refractory CSU in pregnant women

Hypertension

- dihydropyridine calcium channel blockers**: nifedipine**

Thyroid antibodies

- Patients with thyroid autoantibodies and laboratory evidence of clinical hypothyroidism may benefit from thyroid-hormone replacement
- the treatment of euthyroid patients with CSU is controversial

Thanks for your attention