

CHRONIC URTICARIA; *IT'S MORE THAN JUST ANTIHISTAMINES!*

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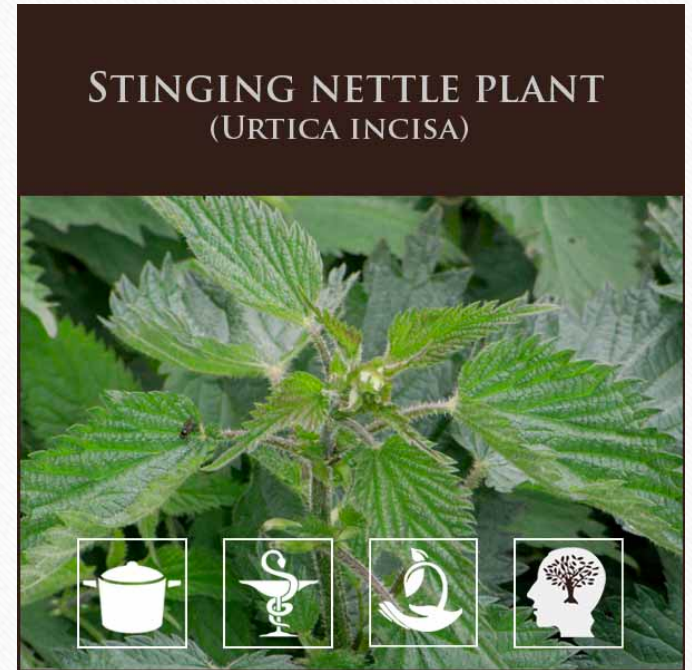
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"I must say, Mr. Jennings, you have the worst case of Hives I've ever seen."

Ūr'tī-kâr'ē-ə

- Urticaria is characterized by intense itching welts caused by allergic reactions to internal and external agents
- From the Latin word *urtīca* which means “nettle”
- “Nettle” refers to any plant from the genus *Urtica*. These plants have toothed leaves covered with hairs that secrete a stinging fluid which effects the skin on contact
- Nettles were used during ancient times as a treatment for paralysis



Features of Urticaria

- Raised, pink/erythematous skin lesions that are markedly pruritic; lesions range from a few millimeters to several centimeters in size and may coalesce
- Evanescent; old lesions go and new ones come over 24 hours leaving no scarring
- Generally worsened by scratching!
- Any area of the body may be involved; most common areas are the
 - perioral and periorbital regions,
 - tongue,
 - genitalia
 - and extremities



Features of Urticaria

- They may vary in size and blanch when pressure is applied.
- An individual hive may last minutes or up to 24 hours and re-occur intermittently in different sites on the body for an indefinite period of time.
- Hives are due to an immunologic reaction in the skin where histamine is released causing the swelling and itching.
- When the hives occur deeper into the skin, it causes more swelling referred to as Angioedema.

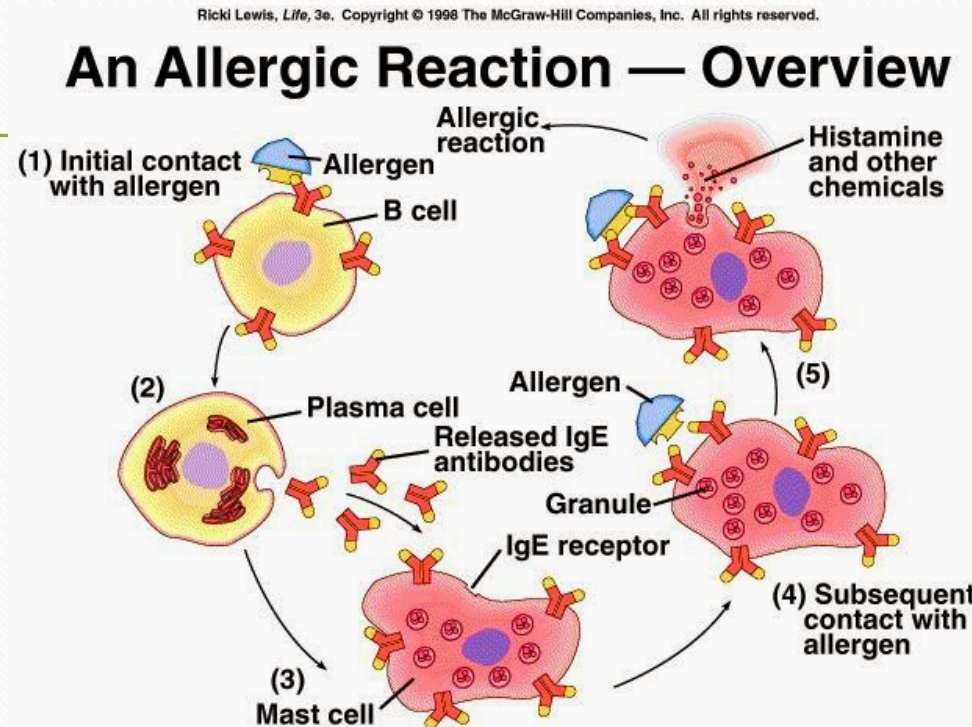


URTICARIA: PATHOPHYSIOLOGY

The mast cell is the major effector cell in urticaria

Immunologic Urticaria: antigen binds to IgE on the mast cell surface causing degranulation, which results in release of histamine

- Histamine binds to H1 and H2 receptors to cause arteriolar dilatation, venous constriction and increased capillary permeability.



Features of Urticaria

- Over 20% of the population will have urticaria at least once in their lifetime. Acute hives may occur in any age group and is most often seen in children.
 - These hives are often self-limited or can be controlled symptomatically with antihistamine drugs and avoidance of identifiable triggers.
- **Chronic urticaria (or chronic idiopathic urticaria) are more common in adults and persist for more than 6 weeks with no identifiable trigger. 1% of the general population. ***
 - 40% have episodes of angioedema, 45% have an autoimmune process associated with anti-thyroid antibodies or high affinity IgE receptor (FceR1) antibody.



* Kaplan AP. Clinical Practice. Chronic urticaria and angioedema. N Engl Med 2002;346:175

Prevalence of Urticaria

- Estimated to occur in 15-23% of the U.S. population
- Up to 40% of patients who have chronic urticaria longer than six months will still have urticaria 10 years later
- Approximately 40% of patients with chronic urticaria have angioedema



Urticaria

- Acute urticaria refers to hives lasting less than six weeks; in approximately 15-20% of cases an inciting cause can be identified
- **Chronic urticaria refers to hives lasting longer than 6-8 weeks; identification of a cause is less than 5%**



Differential Diagnosis:

Immunologic Causes More Often Responsible for Acute Urticaria

- Foods
- Many drugs
- Insect stings
- Transfusion reactions
- Contactants/Inhalants (rare)

**Most common cause of acute urticaria is
—Viral infection!**

Classification of Chronic Urticaria

Most CU is Idiopathic!

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- **Chronic *idiopathic* Urticaria (most common cause)**
 - Sometime called *Chronic Spontaneous Urticaria*
 - **Physical Urticarias** (induced by one or more environmental stimuli)
 - Symptomatic dermatographism
 - Delayed pressure urticaria
 - Cold urticaria
 - Aquagenic urticaria
 - Solar urticaria
 - Cholinergic urticaria
 - Vibratory angioedema and urticaria
 - **Urticarial Vasculitis (<1% of urticaria)**
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Differential Diagnosis:

Non-Immunologic Causes More Often Responsible for Chronic Urticaria

- Physical hives (i.e., dermatographism, pressure, solar, cold...)
 - Hereditary (i.e., cold, heat, vibratory, porphyria, C3b inactivator deficiency...)
 - Vasculitis
 - Neoplasms
 - Infections
 - Endocrine
 - Drugs (i.e., aspirin/NSAIDs-exacerbate hives in up to 30% of cases)
 - Psychologic? *More a myth than fact*
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Features of Physical Urticaria

Type	Age (yrs)	Clinical Features	Angio-edema	Diagnostic Test
Dermatographism	20-50	Linear lesions	No	Light stroking of skin; + transfer factor
Cold (primary vs. secondary)	10-40	Itchy, pale lesions (5% with cryos)	Yes	5-10 minute ice-cube test; + transfer factor
Cholinergic (heat bumps)	10-50	Itchy, monomorphic pale or pink lesions	Yes	Exercise or hot shower; + transfer factor
Pressure	20-50	Large painful or itchy lesions	No	Dermographometer; application of pressure to skin
Solar	20-50	Itchy pale or red swelling	Yes	Irradiation by a solar simulator;+ transfer factor

Tests for Physical Urticaria

Cold	Ice cube test
Localized Heat	Test tube water 44°C
Cholinergic	Exercise for 15-20 min. Leg immersion in 44°C bath
Delayed Pressure	Sand bag test: 15 lb weight for 15 minutes
Dermographism	Stroking skin
Solar	Specific wavelength light exposure
Aquagenic	Water compress
Vibratory	Vortex for 5 minutes

Urticarial Vasculitis:

Features That Differentiate It From CIU

Feature	Chronic urticaria	Urticarial vasculitis
Wheal duration	<24 hr	>24 hr (not always true)
Purpura/pain/hyper-pigmentation	No	Yes
Systemic signs	Usually none	Yes
Laboratory findings	Usually normal	Increased WSR, Acute Phase Reactants; Decreased C3/C4
Leukocytoclasia or extravasation of RBCs	No	Yes
Response to antihistamines	Yes	Sometimes

Chronic Urticaria: The Evaluation

History and Physical Examination

1. Onset (e.g. timing of symptoms with any change in medication or other exposures).
2. Frequency, duration, severity, and localization of wheals and itching.
3. Dependence of symptoms on the time of day, day of the week, season, menstrual cycle, or other pattern.
4. Known precipitating factors of urticaria (e.g. physical stimuli, exertion, stress, food, medications).
5. Relation of Urticaria to Occupation and leisure activities.
6. Associated angioedema, systemic manifestations (headache, joint pain, gastrointestinal symptoms, etc.)
7. Known allergies, intolerances, infections, systemic illnesses or other possible causes.
8. Family history of urticaria and atopy.
9. Degree of impairment of quality of life.
10. Response to prior treatment.
11. General physical examination.

Important to Remember.....

Evaluation of a patient with CU
should involve consideration
of various possible causes!
However, most cases do
NOT have an identifiable cause.

Laboratory Evaluation

- Routine evaluation: *There is no consensus regarding the appropriate tests which should routinely be performed for patients with CU without atypical features by history or physical exam.*
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- Commonly performed tests are:
 - CBC with differential
 - Sedimentation rate and/or C-reactive protein.(If positive run larger ANA panel)
 - Some clinicians routinely perform:
 - Chemistry panel
 - Hepatic panel
 - TSH
 - Anti-microsomal antibodies, anti-thyroglobulin antibodies
 - The utility of performing these tests routinely for CU patients is unclear as studies have demonstrated that they are usually normal and do not affect treatment outcomes.

Evaluation (Continued)

Possible additional evaluation warranted by elements of history or physical exam which would make these tests appropriate:

Functional autoantibody assay (for autoantibodies to Fc ϵ R1) and/or autologous serum or plasma skin testing

(This is a send out to National Jewish because SonoraQuest/LabCorp changed the last 2 years and their CU Index has little meaning)

Complement system: e.g. C3, C4, and CH₅₀

Stool analysis for ova and parasites

H. pylori workup (limited experimental evidence to recommend this)

Hepatitis B and C workup

Chest radiograph and/or other imaging studies

Antinuclear antibody (ANA)

Rheumatoid factor

Cryoglobulin levels

Serologic and/or skin testing for immediate hypersensitivity

Physical challenge tests

Skin biopsy

Urinalysis

Evaluation (Continued)

- Consider more detailed laboratory testing and/or skin biopsy if urticaria is not responding to therapy as anticipated.
- Specific laboratory testing may be required as screening for certain medical therapies that are planned (e.g. G6PD screening prior to Dapsone, hydroxychloroquine)

Treatment Guidelines

- Patient Education
 - Alleviate patient frustration and anxiety
- Reassurance
 - The symptoms of CU can be successfully managed in the majority of patients
- Avoidance of exacerbating factors
 - If known, no external causes can be identified in 80%-90% of cases
- Dietary manipulations
 - For most patient with CU, dietary manipulations are not indicated
 - Undiscovered allergy to food or food additives is NOT likely to be responsible for their symptoms

Table 2. Select Antihistamine Regimens

Antihistamine	Usual Adult Dosage
First-generation antihistamines	
Brompheniramine	8 - 12 mg q12h
Chlorpheniramine	4 mg q6h
Clemastine	1.34 - 2.68 mg q8 - 12h
Diphenhydramine	25 - 50 mg q6 - 8h
Hydroxyzine	25 mg q6 - 8h
Second-generation antihistamines	
Cetirizine	10 mg qd
Loratadine ^a	10 mg qd
Fexofenadine ^a	60 mg bid or 180 mg qd
Desloratadine ^a	5 mg qd
Levocetirizine	5 mg qd
Intranasal second-generation antihistamines	
Azelastine	2 sprays in each nostril bid
Olopatadine	2 sprays in each nostril bid

^a Nonsedating.

H2 antihistamines, taken in combination with first and second generation H1 antihistamines, have been reported to be more efficacious compared to H1 Antihistamines alone for the treatment of UC.

This added efficacy may be related to pharmacologic interactions and increased blood levels of first-generation antihistamines.

Doses of second-generation antihistamines as high as four times the standard dose are advocated in American and most other guidelines on CU (limited studies)

Agents in a Step-Wise Approach

- **H2 antihistamines** (for patients who are not adequately controlled on H1 antihistamines) may experience modest improvement.
 - Hydroxyzine + Cimetidine
 - Cimetidine + Cetirizine ?
 - Ranitidine + Famotidine
- *Until more conclusive data are available, a trial of H2 antihistamines can be considered as additive therapy in pts whose symptoms do not respond adequately to H1 antihistamines alone*

Agents in a Step-Wise Approach

- **Topical Agents**

- Routine use is discouraged
- Rarely result in sustained improvement
- Rarely used as intended
 - Emollients that contain menthol, phenol, or pramoxine (isolated reports)
 - High potency topical steroids (may cause dermal atrophy)
 - Topical antihistamines (doxepin-containing preparations may cause contact sensitization)

Agents in a Step-Wise Approach

- **Systemic glucocorticoids**
 - Usually oral are effective in controlling symptoms
 - Administration beyond several weeks is not justified
 - No evidence that glucocorticoids have a disease-modifying effect
- Most guidelines suggest that oral glucocorticoids be considered as an initial additive therapy for patients with symptoms refractory to one or more antihistamines at full doses.

Agents in a Step-Wise Approach

- **Leukotriene modifiers (useful as monotherapy or add-on therapy)**
 - Believed to involved in the pathogenesis of urticaria
 - Activated mast cells generate and release leukotrienes in addition to histamine
 - Antileukotriene medications include
 - Leukotriene-receptor antagonists:
 - Montelukast
 - Zafirlukast
 - As well as the 5-lipoxygenase inhibitor zileuton

Step 1

- Administer a second-generation antihistamine at standard therapeutic dose
 - Avoid NSAIDS/other triggers/exacerbating factors

Step 2

- If Step 1 does not control symptoms within one to two weeks increase therapy by one or more of the following:
 - Advance the dose of second-generation antihistamines (up to 4 X standard dose)
 - Use different second-generation antihistamine
 - Add H2 antihistamine
 - Add a leukotriene-receptor antagonist
 - Add a first-generation H1 antihistamine at bedtime

Step 3

- If measures in Step 2 do not result in adequate control of symptoms:
 - Advance gradually doses of H1 antihistamines
 - D/C any medications that were added in Step 2 that did not appear to benefit the pt

Step 4

- Patients whose symptoms are not controlled by Step 3 or who are intolerant of dose advancement of first-generation H1 antihistamines are considered to have refractory CU
- Consider including anti-inflammatory immunosuppressive agents
 - Omalizumab
 - Cyclosporine

When to Refer

- An underlying disorder is suspected
 - Refer to allergist/immunologist
- S/S suggest urticarial vasculitis
 - Refer to specialist capable of performing skin biopsies
- Symptoms are not controlled with Steps 1-3 or Pt is requiring repeated or prolonged treatment with glucocorticoids
 - Refer to allergist/immunologist

QUESTIONS/DISCUSSION



References

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