Allergic Urticaria: Acute and chronic diagnosis and management

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Disclosures

- Speaker's Bureau for Abbvie, Beiersdorf, Eli Lilly, Janssen, Sanofi Genzyme, Sanofi-Aventis/Regeneron®, and Sun Pharma
- Strategic Advisor and Medical Board Member: Arcutis Biotherapeutics, Incyte Labs, Leo Pharma, and Novartis.
- No experimental or investigational use of drugs or devices will be presented.

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Objectives

- At the end of this presentation, the participant will be able to:

1. Develop strategies for making the correct diagnosis of acute and/or chronic allergic urticaria and subsequent management.
2. Interpret data for evidence-based therapies in use for acute and/or chronic urticaria.
3. Implement strategies for prevention of ongoing flares and identifying triggers for acute and/or chronic urticaria.

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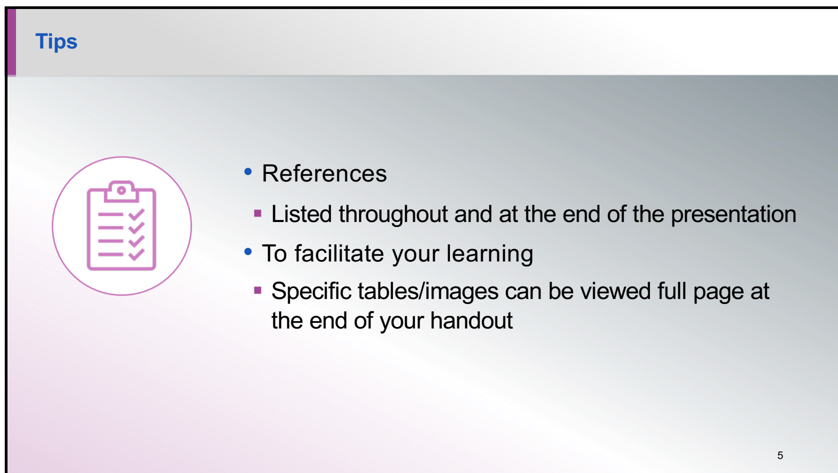

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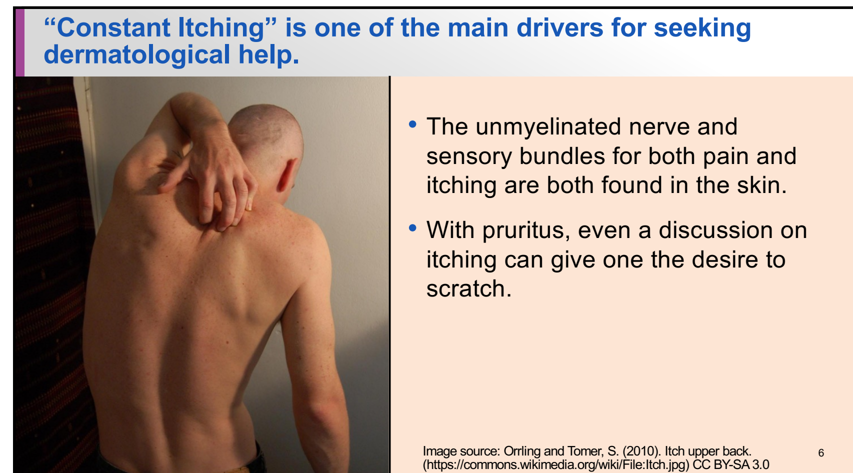

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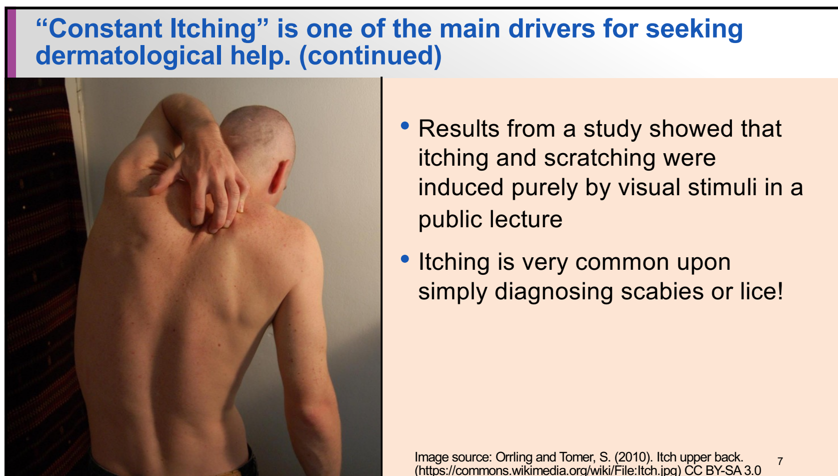

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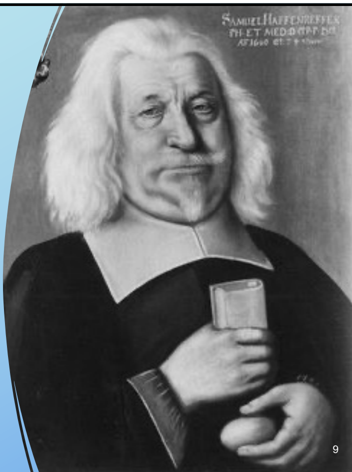
Samuel Hafenreffer:
Father of Itching

German physician, who in 1660 first identified pruritus as an official medical condition, as it produces an "unpleasant sensation" in the skin, when provoked to scratch.



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People are looking for help on social media.

- One study of Instagram found advertisements for oral over-the-counter non-FDA regulated supplements, most common conditions: Hair loss/growth (31%), acne (20%), aging (14%), hyperpigmentation (13%), and wrinkles/fine lines (7%).
- Authors found a lack of complete ingredient data, but when listed, could be responsible for secondary pruritus.
- Are we always clear as to what our patients are using for their health?

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False advertising for health is common and persistent.

A Woman's Face Is Her Fortune.

DR. SIMM'S ARSENIC COMPLEXION WAFERS

After a few days' use will permanently remove all Blotches, Moles, Pimples and Freckles, producing an Entrancingly Beautiful Complexion that shames the use of powders and creams. Warranted perfectly harmless. Sold by all leading druggists at $1 per box of 100 wafers.

Dr. Simms' Safe Periodical Wafers are sure and reliable for all female irregularities. Price $2 per box. Sent by mail (secure) on receipt of price. Warranted to contain no "Tansy" for "Pennyroyal."

THUMLER & Co., 83 Chambers St., New York.
H. M. Parchen & Co., Sole Agents, Helena.

ELECTRICITY A NATURAL CURE!

NO MORE USE FOR CRUTCHES OR DRUGS.

TAKE A TREATMENT FREE!

I have so adapted my application of medical electricity that I positively cure Rheumatism, Kidney and Stomach Troubles and all affections of the vital organs. To illustrate the remedial power of my

Dr. McLaughlin's Belt

I will give you a free treatment in my office by the galvanic current from my grand stationary battery. This is a breezy and exhilarating test of that curative power now used the world over.

To cure your ailment I will fit you with one of my famous Belts, which you wear at night until your system becomes charged with the reviving voltage. This keeps up the action of the blood vessels, contracts and strengthens relaxed muscles and glands. It casts out impurities, which are the cause of pain, and restores to the body its wonted energy. You feel the glow, the enlivening sensation of this power from the start. The improvements my Belt possesses above all others are recognized and appreciated by the thousands who are using my appliances. The cures I have made, the testimony from all quarters, the comfort of wearing my Belt, the method of adjusting the power, its thoroughly curative work, constitute it the pre-eminent remedy for the severest pain or the most trying weakness.

Rheumatism and Kidney Trouble.
197 Henry St., San Francisco, Jan. 14, 1900.
DR. M. A. McLAUGHLIN—Dear Sir: I am now perfectly cured of all my pains and from the first time of using your Belt I have been able to keep up at my work.
Yours respectfully,
DANIEL MULLER (Cooper).

Call and take a treatment free from my Static Battery and test my Belt, or let me send you my new book, free.

DR. M. A. McLAUGHLIN,
702 Market Street, Corner Kearny, S. F.
NEVER SOLD IN DRUG STORES.

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Electricity a Natural Cure. (1900). In the public domain due to over 100 years past publication.

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Why am I itching? The Longest Lists in Healthcare

- Foods: Absolutely any food can qualify for anyone, but…
  - Nuts, seafood, shellfish, dairy, chocolate, tomatoes, berries, and grains are common.
  - Pineapples, strawberries, processed meats and white wines

- **Pearl:** Fresh food more likely than cooked, and don't discount additives and preservatives

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Why am I itching? The Longest Lists in Healthcare (continued)

- Medications: Any medication can induce an urticarial response, but…
  - Common for blood pressure, opioids, fentanyl, statins and diabetes medication to cause itching
  - Vaccines

- **Pearl:** Never allow a patient to convince you that it's not a medication they have been using for many years.
- Infections: Viral, bacterial, fungal, yeast, autoimmune

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Common Sources of Itching: Seborrheic Dermatitis or "Cradle Cap"

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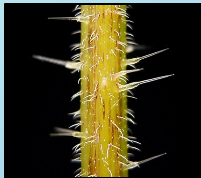
Seasonal allergies and reactions can occur with what is in the garden.



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Why am I itching? The Longest Lists in Healthcare (continued)

- Infestations: Lice, demodex mites, ticks, scabies, chiggers and water parasites
- Environmental: Sunshine, heat, cold, pressure, water, topical skin triggers, grass, animal dander, dust, dust mites, and tree pollens
- Allergic: Urushiol oil in poison ivy/oak/sumac/mango, nickel, lanolin, parabens, fragrance, rubber

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Why am I itching? The Longest Lists in Healthcare (continued)

- Skin disorders
  - Atopic dermatitis, psoriasis, seborrhea, athlete's foot, hidradenitis, tendency to keloid, seborrheic keratosis
- Medical disorders
  - Diabetes, thyroid, neuropathy, xerosis, psychiatric, anemia, cholestasis
- Pregnancy
  - Pruritic urticarial papules and plaques of pregnancy (PUPPP), gestational pemphigoid, xerosis

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Mythbusters: Does Spanish moss harbor chiggers?

- An old wives' tale in the southern USA is that Spanish moss in trees contains chiggers.
- Entomologists have never found chiggers in Spanish moss on trees, even despite repeated attempts; nor have they found red mites (the adults).
- But chiggers are present on lower grasses and animals.

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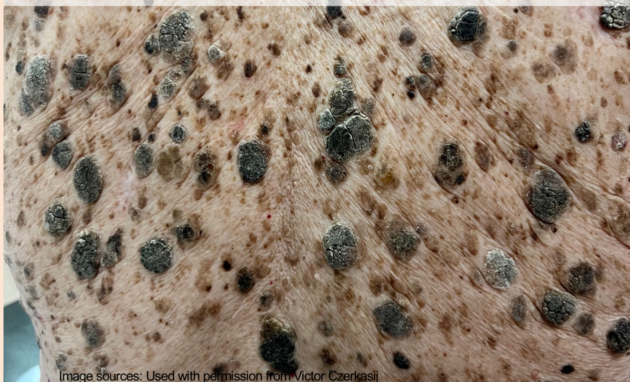
Common conditions which are not life-threatening can create significant itching.



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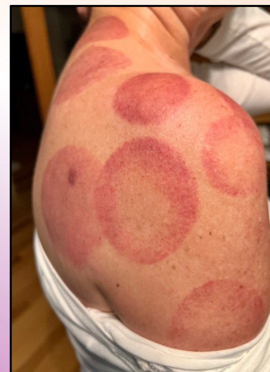
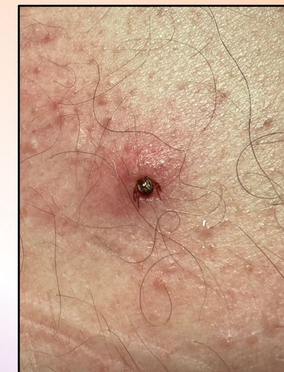
People are turning to ancient "cupping" techniques for their relief of hives. Ticks are a major source of urticarial breakouts.





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Why am I itching? The Longest Lists in Healthcare (continued)

- Menopause: Hormonal changes and imbalances
- Stress: Increase of histamines correlates with blood pressure

- Terminal illness: Cancers can induce enzyme and cytokine storms.
- Idiopathic: Up to half of patients and providers cannot find a cause.
- Speaking of ticks…

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Alert: Tick Bites and Alpha-Gal Syndrome

- A life-threatening food allergy triggered by tick bite is affecting hundreds of thousands of people in the U.S.

- Known as “tick bite red meat allergy”, it begins with a bite from Lone Star ticks, found in Southeastern and East.

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Alert: Tick Bites and Alpha-Gal Syndrome (continued)

- The tick’s saliva contains a sugar molecule called alpha-gal, which is injected into the body with the bite.
- This triggers allergies to certain types of red meat (primarily pork, beef, rabbit, lamb or venison) or products made from mammals (including cheese, milk, other dairy products and gelatin).

- When people eat any foods containing the allergens, they can experience serious allergy symptoms within a few hours.

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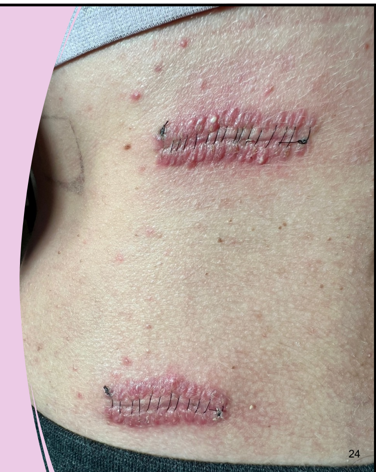
Common Reaction to Nylon Sutures

Pearl: Redness isn’t always infection; consider inflammation.



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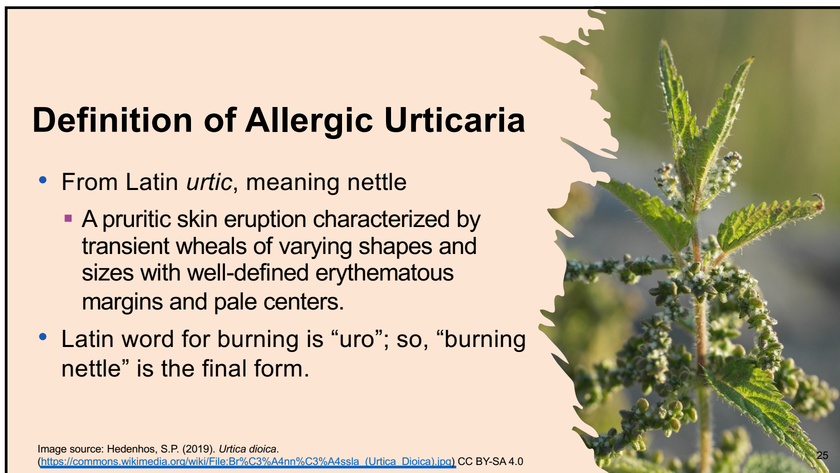

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Major Categories of Urticaria

- Acute: Considered less than 6 weeks
- Chronic spontaneous urticaria (CSU): More than 6 weeks
- Chronic inducible urticaria (CIU): More than 6 weeks but episodic, also known as dermatographic

- Physical urticaria: Triggered by water, cold, pressure, heat, vibratory, contact, cholinergic, or episodes of stress
- These types of breakouts are important categorizations to understand course of treatment

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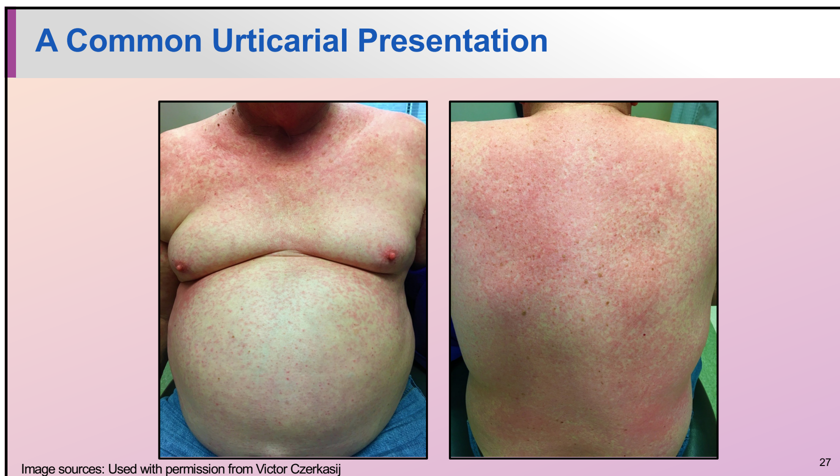

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The Burden of Urticaria

- **One in five** Americans may develop some form of urticaria in their lifetime.
- Urticaria may occur at any age, but acute spontaneous urticaria is more common in childhood, while chronic idiopathic urticaria (CIU) is more common in the fourth and fifth decades.
- Females are 2 >1 for CIU, but F=M for all other types.

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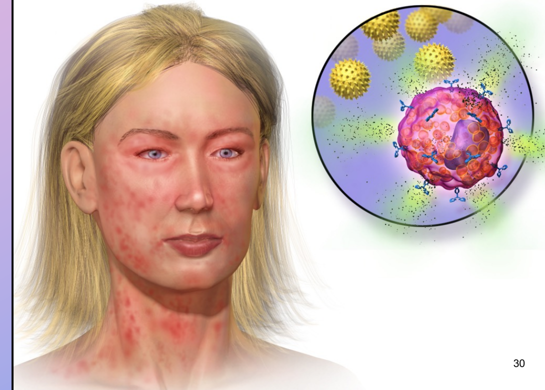
We Know What Occurs But Need to Know Why

- A mast cell (or mastocyte) is a resident granulocyte of the connective tissue.
  - Rich in histamines
- Important place in the immune system playing a protective role in wound healing and defense against pathogens



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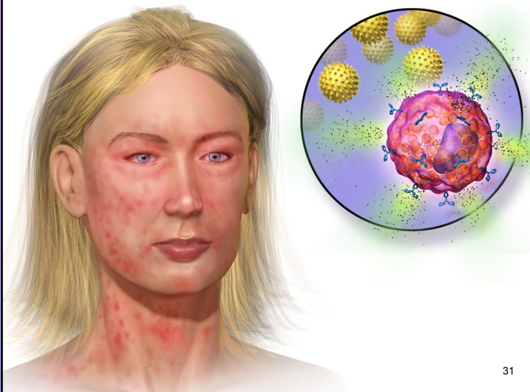
We Know What Occurs But Need to Know Why (continued)

- However, an over-proliferation of mast cells in the presence of a trigger can also induce histamine release, responsible for itching, edema, allergies and anaphylaxis.



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The Mosquito Bite – A Common Example of Histamine Release

- Papular urticaria is regarded as a symptom of a common mosquito bite allergy manifested in individuals with one of the other mosquito bite allergies.
- Mosquito saliva contains >30 potentially allergenic proteins.

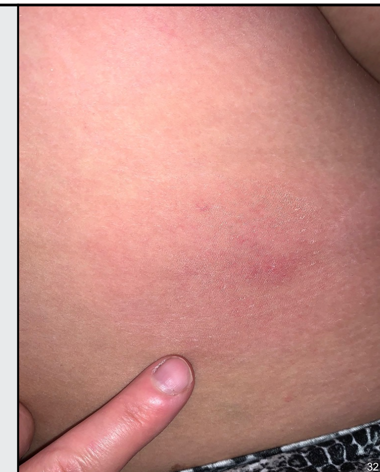

Image source: Nurse90. (2020). Severe mosquito bite reaction. (https://en.wikipedia.org/wiki/File:Severe_mosquito_bite_reaction.jpeg) CC BY-SA 4.0

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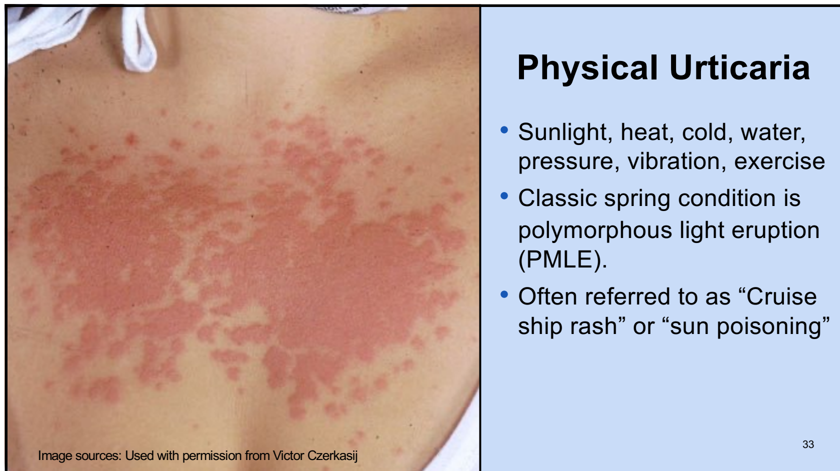

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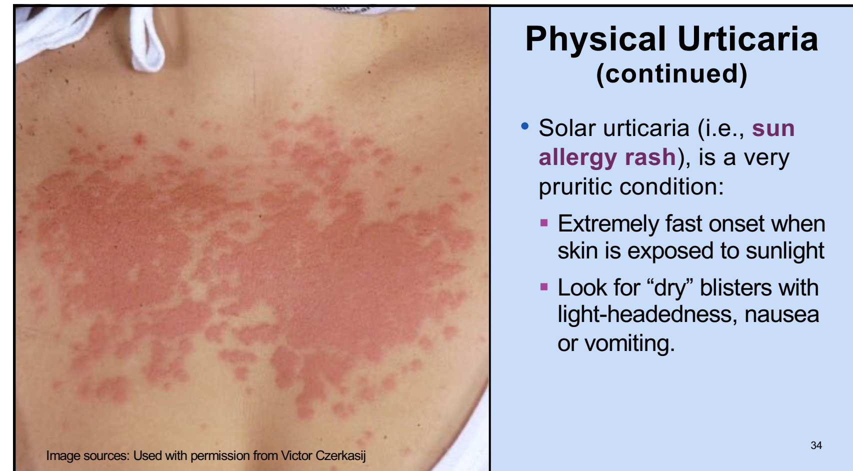

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NP Training: Prevention and lifestyle choices are key components to avoid breakouts.

- Counsel your patients to understand their dietary triggers.
  - Avoid inflammatory choices.
- Sunscreen SPF 30 and reapplication is helpful.

- Lessen stress and anxiety where possible.
  - It’s often of our making, and how we respond.
- Where can lifestyle and diet take the place of medications?
- Loose-fitting clothing, better bathing, and discuss the option of targeted systemic biologics.

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NP Training: Prevention and lifestyle choices are key components to avoid breakouts. (continued)

- Sleeping regularly and deeply is anti-inflammatory.
  - Avoid the internet, phone screens, and stress before bedtime.
- Get early morning sunlight exposure.

- Walk daily as a healthy immune system lessens inflammation.
- Remember flavonoid antioxidants found in colorful fruits and vegetables.
  - Vitamin D and zinc supplements have been shown to help, as can lower caffeinated green tea.

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NP Training: Prevention and lifestyle choices are key components to avoid breakouts. (continued)

- Ground flax and olive oil are full of omega-3.
- Ginger, cinnamon, cumin, coriander and turmeric are under deep study as anti-inflammatories.

- Probiotics foster good gut health.
  - Try yogurt, sauerkraut, kimchi, miso, and kombucha.

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Pressure-induced Urticaria

- Extremely rare and frustrating
  - Standing, walking, wearing bra (seen previously), tight clothes, carrying a purse, sitting or leaning on a hard surface, compression stockings, intercourse, tampon use, wearing eyeglasses or jewelry, watch-bands, tool handling and other triggers can cause very itchy hives.
  - Don't carry eight shopping bags on the wrist from the car in one trip!
- Many mediators under investigation.

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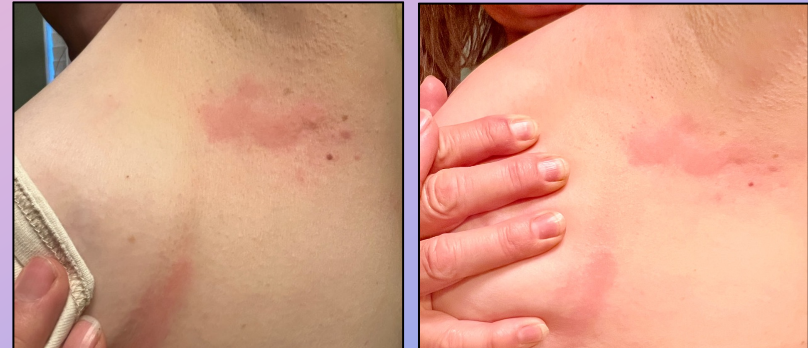
Pressured-induced Urticaria



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Cold Urticaria

- Triggers include swimming in cold or hot water which leads to rapid drop or increase in blood pressure, resulting in fainting or shock.
- Can also occur when warming after cold exposure or drinking a very cold beverage
  - Some have "brain freeze" headaches, but this can be anaphylactic.
- Cold urticaria occurs most frequently in young adults.

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Cold Urticaria (continued)

- A whole-body response (anaphylaxis) is dangerous, with swelling limbs, tongue, throat or shock soon after exposure to cold, or even very damp air.
- Full skin exposure could lead to loss of consciousness.
- Epinephrine autoinjector important tool in person's arsenal.

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Pearls for Providers

- If a patient is becoming established, have them bring pictures of the rash and determine frequency, positioning and degree of severity.

- Try to understand how it occurs, and what may trigger it.
- Ask "what has made it better?" How long does the flare last?

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Pearls for Providers (continued)

- Generally painless without systemic signs.
  - Lab values are often normal.

- Ask if the patient has other comorbidities, particularly allergies, asthma, and whether there are animals in the house.
  - History – as much as you can – drives diagnosis.

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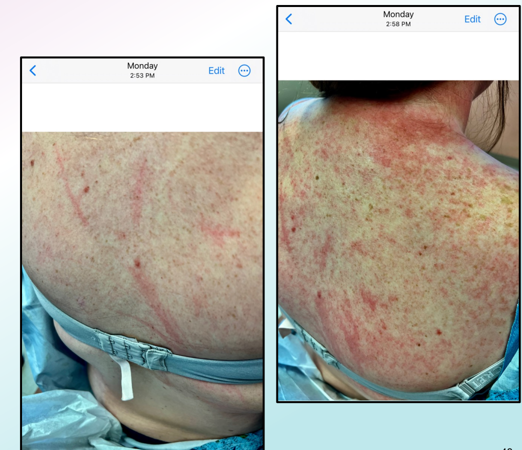
The Speed of Hives: Observe the Time Stamp



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Alert! The Occurrence of Angioedema

- Angioedema is a descriptive term for deep swellings of the dermis, subcutaneous and submucosal tissues.

- Usually painful rather than itchy, poorly defined
- Can be reddish or violet, depending on skin color, or no change from normal color

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Alert! The Occurrence of Angioedema (continued)

- Swelling is under the skin instead of on the surface and can be significant causing difficulty breathing or seeing.
- Hives are often called welts.
  - They are a surface swelling.

- It is possible to have angioedema without hives.
- Anaphylaxis is sudden, severe, systemic, and life-threatening.

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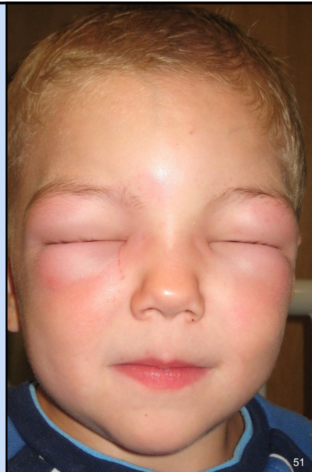
Periorbital Angioedema



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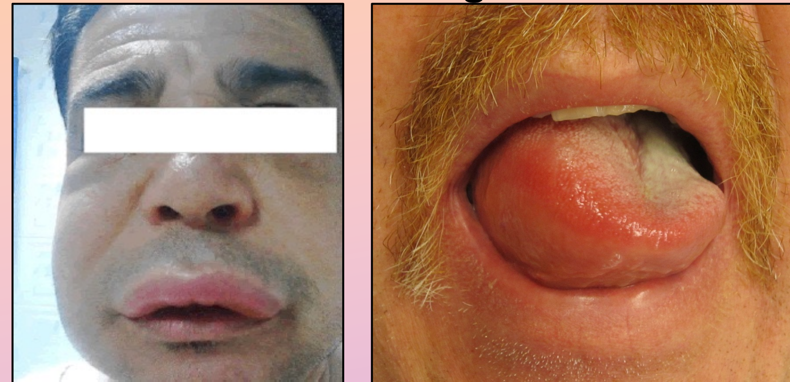
Submucosal Angioedema



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Angioedema is life-threatening to airways.

- Corticosteroids and antihistamines are first-line treatment.
- Epinephrine injections – People with a history of anaphylaxis
- Some individuals carry inhaler medicines that help open up the airways.

- H_1-antihistamine hydroxyzine is most potent of the classic antihistamines.
- 2nd-generation low sedation H_1-antihistamines 10 mg cetirizine and 5 mg levocetirizine are potent.

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Angioedema is life-threatening to airways. (continued)

- Fexofenadine and loratadine are well tolerated.

- In summary, first-line treatment is 2nd-generation antihistamines at high doses, but failure rate is about half.

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Summary of Chronic Idiopathic Urticaria

- No specific trigger, lasts six weeks or longer and up to five years and in some cases for decades
- Creates anxiety, sleeplessness, lack of energy, social isolation, and emotional upset
- Women can suffer at double the rate over men.
- Requires dietary and lifestyle changes and interferes with careers, professions, hobbies, personal pursuits, and family experiences

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First-line Treatments for Allergic Urticaria: The History of Antihistamines

- The first true antihistamine 1940s is diphenhydramine (Benadryl®) but rarely used in dermatology.
- Weak as an antihistamine, heavy on sedating effect, short half-life, but easily available and familiar to parents
- Prescription hydroxyzine (Atarax®) is sedating; anxiolytic antihistamine that is non-habit-forming since the 1950s

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First-line Treatments for Allergic Urticaria: The History of Antihistamines (continued)

- Dosing should always follow manufacturer's recommendations; however, allergists can override dosing based on trial data and experience if the presentation warrants an increase.
- Four-fold increases in H_2-antihistamines for up to two weeks has become common practice.

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Guideline Recommended Step Care

- First-line antihistamines (i.e., doxepin, diphenhydramine or hydroxyzine)
- Initiate 2nd-generation antihistamines (i.e., cetirizine, desloratadine, fexofenadine, levocetirizine, or loratadine).
  - Avoid known triggers and NSAIDs.

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Guideline Recommended Step Care (continued)

- Second-line
  - If symptoms persist after two weeks, increase dose four-fold and add another 2nd-generation antihistamine as previously referenced ***or*** an H_2 blocker (ranitidine, famotidine, cimetidine).
  - Steroid initiation can be combined in first- and second-line therapy. Consider a systemic approach with topical.

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Guideline Recommended Step Care (continued)

- Third-line: This is going to require some discussion…
  - If symptoms persist another approximate two weeks, discontinue what doesn't seem to be working, and begin 1st-generation antihistamine at bedtime due to sedation.
  - Should we biopsy? Is it allergic urticaria? What are some important differentials? Primary care is quick to order blood work: What are we looking for?
  - The road forks here: Immunosuppressants or referral?
- If not improved after two weeks, consider a referral to a dermatology or allergy specialist.

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Guideline Recommended Step Care (continued)

- At the allergist, cyclosporine (anti-inflammatory, immunosuppressive) or omalizumab (monoclonal antibody that specifically binds to IgE) will most likely be implemented.
- At this point, biologic omalizumab has proven very effective when initiated.
- Biologics are specialty medicines that are made inside living cells that target specific parts of the immune system involved in the disease.
- Often injectables, to bypass the stomach enzymes

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Summary: Approved Oral Adult Dosing of 1st-generation H_1 Blockers

- Diphenhydramine 25–50 mg daily
- Hydroxyzine 10–25 mg up to 3 × day
- Doxepin 25–50 mg at bedtime, but only for 1–2 weeks

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Summary: Approved Oral Adult Dosing of 2nd-generation H_1 Blockers

- Cetirizine 10 mg daily
- Desloratadine 5 mg daily
- Fexofenadine 180 mg daily to BID
- Levocetirizine 5 mg daily to BID
- Loratadine 10 mg daily

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Approved Oral Adult Dosing of H_2 Blockers

- Cimetidine 300 mg BID
- Famotidine 20 mg BID
- Ranitidine 150 to 300 mg BID

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What is a 2nd-generation antihistamine?

- Loratadine (Claritin®) OTC, generally nonsedating and well-tolerated
- Cetirizine (Zyrtec®) OTC, asthma and allergist favorite, often doubled at 10 mg 1 PO BID for a week in flares
- Desloratadine (Clarinex®) Rx, long-lasting effect, improves acne

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What is a 2nd-generation antihistamine? (continued)

- Levocetirizine (Xyzal®) Rx, better for hay fever, doesn't prevent histamine release, few head-to-head studies
- Fexofenadine (Children's Allegra®) OTC, excellent safety profile, available age 2 years and older
- Reminder – The **"D"** is "decongestant" as in **pseudoephedrine**.

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Guideline Recommended Step Care (continued)

- Rescue therapy
  - Corticosteroids should be implemented for a maximum of ten days.
- Alternative treatments not tested in randomized controlled trials (RCT) include dapsone, hydroxychloroquine, sulfasalazine and methotrexate.
  - Discussion to follow

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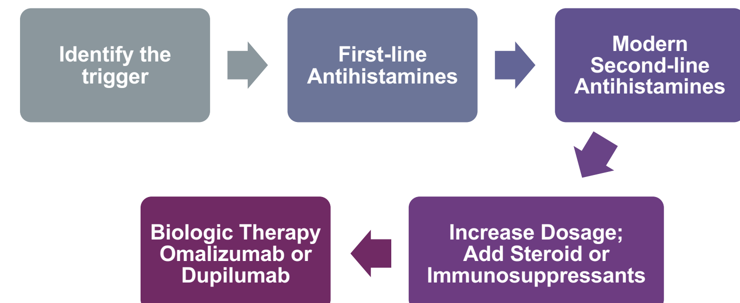
Can we improve on this step therapy?



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Omalizumab (Xolair®) for CIU

- First injectable subcutaneous monoclonal antibody made similar to natural antibodies created in human body
  - Indicated for age 12 years and older
  - Approved in 2014
  - 60% of patients achieved at least a 50% improvement in first three months
  - 50% of patients achieved 100% resolution

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Omalizumab (Xolair®) for CIU (continued)

- Dosing
  - 300 mg/150 mg monthly injections, dependent on weight
  - Blackbox warning for anaphylaxis in 0.1% of patients, but general population lifetime risk is about 2% for bee stings, consuming shellfish or drug reaction.

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How Omalizumab Works

- Omalizumab binds to IgE
  - Early immune system defense reaction immunoglobulins
  - Before they can attach to mast cells and trigger histamine, releases and reduces the number of IgE receptors on mast cells
- Common early adverse effects are nausea, headaches, cough and joint pain.

- Therapy is often discontinued at 6–12 months but it is variable.
- Excellent established option for CIU patients.
- Referral is often to allergists and asthma specialists.
  - Not a medication marketed to dermatology

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Cochrane Review for Clinicians

- 73 studies with 9,759 participants
  - Best evidence – Cetirizine (Zyrtec®) 10 mg daily
    - Most effective at complete suppression of CIU
  - Loratadine (Claritin®) 10 mg daily vs. placebo
    - Found no difference
  - Levocetirizine (Xyzal®) 5 mg
    - Effective in intermediate, but not short-term

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Cyclosporine (Neoral®)

- Very effective in CIU with 80% response rate in double-blind, placebo-controlled trials
- 100 mg 1 PO BID for three months with tapering to daily
  - 50 mg daily then 25 mg daily and then 25 mg per month

- Must monitor BP, renal function
- This is considered as a front-line rescue drug and not for regular use.

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Cyclosporine (Neoral®) (continued)

- Recommend blood/urea/nitrogen (BUN), creatinine, urinalysis and BP at start of therapy and repeat monthly.

- Contraindicated in HTN and renal dysfunction but helpful in those with diabetes who have normal renal function and cannot use corticosteroids.

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The Balance of Corticosteroids

- High doses for **protracted times** are not recommended, as adverse effects clearly exceed benefits.
- However, in CIU 10–20 mg 1 PO daily or every other day is helpful and can be tapered over a course of a month.
- Corticosteroids can be used rationally.

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Methotrexate, Dapsone, Hydroxychloroquine, and Sulfasalazine

- The safest and most appropriate statement is that these familiar anti-inflammatories are effective in disorders other than CIU.

- Extrapolation is at the providers discretion and in risk/benefit discussions.
  - No studies in CIU
  - Not necessary anymore in light of the excellent biologic options

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The Dilemma of Doxepin

- Doxepin is used for depression, anxiety, sleeplessness and pruritus. It is helpful in CIU, but habit-forming.
- Doxepin oral formulation FDA-approved for short-term management (up to eight days) of atopic dermatitis and lichen simplex chronicus.
- Long serious adverse effects panel.

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The Promise of Dupilumab

- Monoclonal antibody biologic that blocks IL-4/IL-13
- Approved for atopic dermatitis, (eczema), asthma, nasal polyps (chronic sinusitis) and prurigo nodularis or “pickers disease” aka “neurotic excoriation”
- Awaiting approval from FDA for chronic obstructive pulmonary disease (COPD) and allergic urticaria
- In eczema, approved for age 6 months and older with injection dosing dependent on age and weight

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The Promise of Dupilumab (continued)

- Not considered a classic immunosuppressant, as no labs required prior to initiating or while using the medication
- Adverse effects include allergic reaction, conjunctivitis, and reactivation of cold sores

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Personal Observations

- Reminder: Worst food triggers include shellfish, seafood, nuts, chocolate and dairy.
- Medications most implicated are blood pressure, statins, antibiotics, and metformin.

- Ongoing stress or new, dynamic event
- Liver and kidney challenges
- Remember – Biopsy doesn’t tell us **which**

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Review the Key Components: Be the Detective!

- **Onset**
  - Questions of timing, medication changes and exposures
- **Duration**
  - Frequency, severity and location on your body?

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Review the Key Components: Be the Detective! (continued)

- **Patterns**
  - Does this occur only while at work? Do you observe this as seasonal? Is it more common with your menstrual cycle or a time of day or time of week?
  - What do you believe calms the condition or makes it worse?

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Review the Key Components: Be the Detective! (continued)

- **Precipitating factors**
  - Exertion, foods, work responsibilities, stress-events, family outings or social events
- **Activity**
  - Occupation or leisure? Does it occur when alone at home or exertion with activities?

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Review the Key Components: Be the Detective! (continued)

- **Systemic associations**
  - Headache, joint pain, gastrointestinal symptoms, photophobia, or disorientation?
- **Family history**
  - Genetics and having others suffer is a key

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Review the Key Components: Be the Detective! (continued)

- **Treatment**
  - History of failures, successes
  - Scabies still lurk in all age groups as a possibility
- **Quality of life**
  - What is the worst or ultimate effect on your life? How has this impacted your relationships, work or studies?

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The Rare Referral in Dermatology

- Dermatology is often "the end of the road" for most patients, with high success rate in diagnosis and treatment using our current technologies.
- Besides oncology and rheumatology, **allergists** are our most helpful partners in dermatology.

- Consider partnering; share a lunch; spend a morning shadowing.
- Remember: If you can still help the patient without ever knowing why, it reduces stress to stop dwelling on that issue.

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End of Presentation
Thank you for your time and attention.

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