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Testing for Inducible Urticarias

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Learning Objectives

- Review the clinical presentation of chronic inducible urticaria
- Where applicable, identify subtypes and differential diagnoses
- Discuss techniques for provocation testing and interpret their results

Classification of Urticaria

| Type | Subtype | Definition |
|--|-------------------------------|--|
| Spontaneous urticaria | Acute spontaneous urticaria | Spontaneously occurring wheals and/or angioedema for <6 weeks |
| | Chronic spontaneous urticaria | Spontaneously occurring wheals and/or angioedema for 6 weeks or longer |
| Type | Subtype | Precipitating factors |
| Inducible urticaria or physical urticaria | Cold urticaria | Cold objects, air, fluids, wind |
| | Delayed pressure urticaria | Vertical pressure (stimulates wheal reaction within 3-12 hours) |
| | Heat urticaria | Localized heat |
| | Solar urticaria | Radiation from ultraviolet and/or visible light |
| | Symptomatic dermographism | Mechanical shearing forces (stimulates wheal reaction within 1-5 minutes) |
| | Vibratory angioedema | Vibratory forces such as pneumatic hammer (stimulates wheal reaction within 1-2 hours) |
| | Aquagenic urticaria | Water |
| | Cholinergic urticaria | Increasing core body temperature |
| | Contact urticaria | Contact with substance that predisposes patient to wheal reaction |

Symptomatic Dermographism (SD)

- Is the most common CIndU (adults 50–78%, children 38-65%).^[2,3]
- More common in young adults (mean onset 26 yo).^[4]
- Histamine release is triggered by firm stroking, friction, scratching, shear force, or trauma.^[2,5]
- Lesions and itch usually begins within 5 min of stimulation and persists for 15–30 min.^[6]
- May also be precipitated by the pressure (elastic in underwear or shower jets).^[7]
- Overheating, stress, and anxiety usually aggravate symptoms.^[6]



2. Pozderac I, et al. *Acta Dermatovenerol Alp Pannonica Adriat.* 2020 Sep;29(3):141-148.
3. Bal F, et al. *Pediatr Allergy Immunol.* 2021 Jan;32(1):146-152.
4. Rustin, MHA, Orteu, CH. In [Encyclopedia of Immunology \(Second Edition\)](#) 1998
5. Kaufman A, Rosenstreich DL. *Ann Allergy.* 1990 Nov;65(5):367-73.
6. Siegfried EC, Hebert AA. *J Clin Med.* 2015 May 6;4(5):884-917
7. Grattan CEH, Borzova E. In [Clinical Immunology \(Fifth Edition\)](#) 2019

SD Rare Subtypes

- **Red dermatographism:** repeated rubbing is necessary to induce erythematous bands.^[8]
- **Follicular:** urticarial papules elicited by stroking, especially around hair follicle.^[8]
- **Cholinergic:** manifests similarly to cholinergic urticaria, with a large erythematous line marked by punctate wheals.^[2]
- **Cold-dependent:** observed only with chilling the skin before or after scratching.^[8,9]
- **Delayed:** appears 3 to 8 hours after the initial trigger and persists 24-48 hours, not always preceded by an immediate wheal-and-flare ^[2,6]
- **Food-dependent:** dermatographism only after the intake of food, not before.^[10]



Follicular dermatographism ^[8]

2. Pozderac I, et al. *Acta Dermatovenerol Alp Pannonica Adriat.* 2020 Sep;29(3):141-148
6. Siegfried EC, Hebert AA. *J Clin Med.* 2015 May 6;4(5):884-917
8. Mecoli CA, Morgan AJ, Schwartz RA. *Cutis.* 2011 May;87(5):221-5
9. Kaplan AP. *J Allergy Clin Immunol.* 1984 Apr;73(4):453-6
10. Ertaş R et al. *J Allergy Clin Immunol Pract.* 2023 Mar;11(3):932-940

SD Mimic: Simple Dermatographism

- Simple dermatographism is generally asymptomatic
- Is a manifestation of the “Triple response of Lewis,” a physiologic response to trauma involving a red line (capillary injury), flare (axon-reflex vasodilation of arterioles), and linear wheal (transudation of fluid from injured capillaries).^[11]
- Occurs in approximately 2 to 5% of the general population.^[3]
- This response may be absent in patients with axonal or brachial plexus injuries.^[12]



Negative Triple Response of Lewis after brachial plexus injury^[12]

2. Pozderac I, et al. *Acta Dermatovenerol Alp Pannonica Adriat.* 2020 Sep;29(3):141-148

11. Paller AS, Mancini AJ. In Hurwitz Clinical Pediatric Dermatology (Fourth Edition), 2011

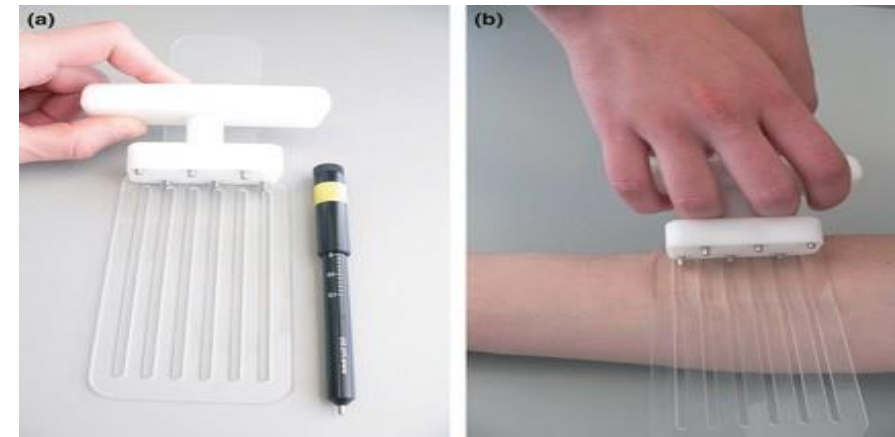
12. Sterman-Neto H, et al. *Interdisciplinary Neurosurg.* 2020 June;(20) 100637

SD Diagnosis: Dermographometer

- A dermographometer is a handheld device with a spring-loaded tip, originally designed by Bettley in 1962.^[13,14]
- A six-pronged dermographometer that allows for simultaneous dermal stimulation with six different provocation levels: three above and three below 36 g/mm² ^[13]



Calibrated dermographometer set to 3 kg/cm² ^[14]



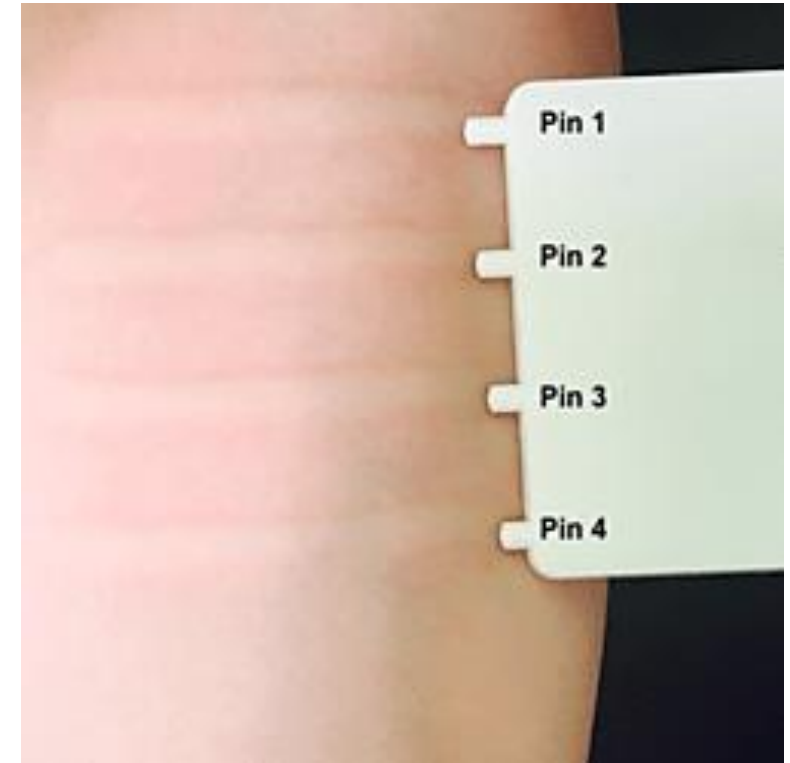
Six-pronged dermographometer ^[13]

13. Mlynek A, et al. *Clin Exp Dermatol*. 2013;38:360

14. Wallengren J, Isaksson A. *Acta dermato-venereologica*. 2007;87(6) 493-8.

SD Diagnosis: FricTest

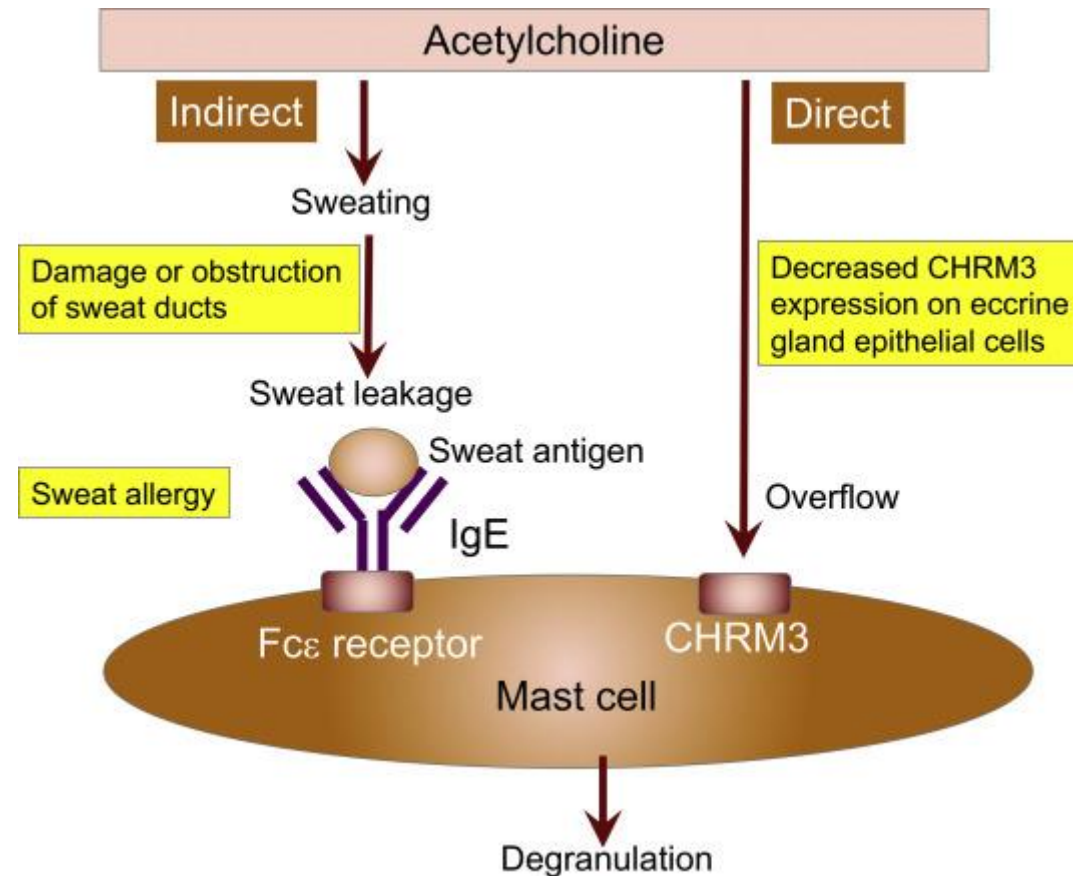
- Provocation and threshold testing can also be performed with FricTest, a dermatographic tool.^[10,15,16]
- Four tips are 3.0, 3.5, 4.0, and 4.5 mm in length.^[15,16]
- Result deemed positive if a pruritic wheal of ≥ 3 mm width is present within 10 minutes after provocation.^[15]
- Threshold triggers correlate with QoL, pruritus, and disease severity.^[15,16]



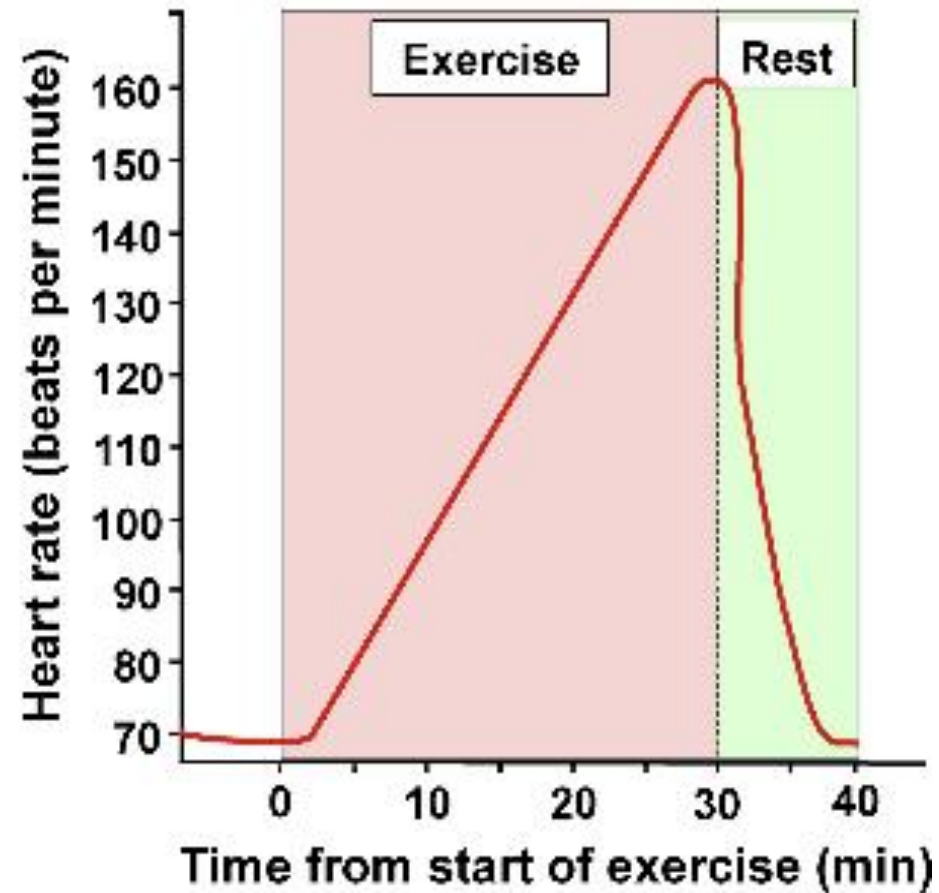
The FricTest ^[15]

10. Ertas R et al. *J Allergy Clin Immunol Pract.* 2023 Mar;11(3):932-940
15. Maurer M, Fluhr JW, Khan DA. *J Allergy Clin Immunol Pract.* 2018 Jul-Aug;6(4):1119-1130
16. Can PK, et al. *Int Arch Allergy Immunol* 2019; 178: pp. 76-82.

Cholinergic Urticaria (CholU)



CholU Testing: Pulse-controlled Ergometry



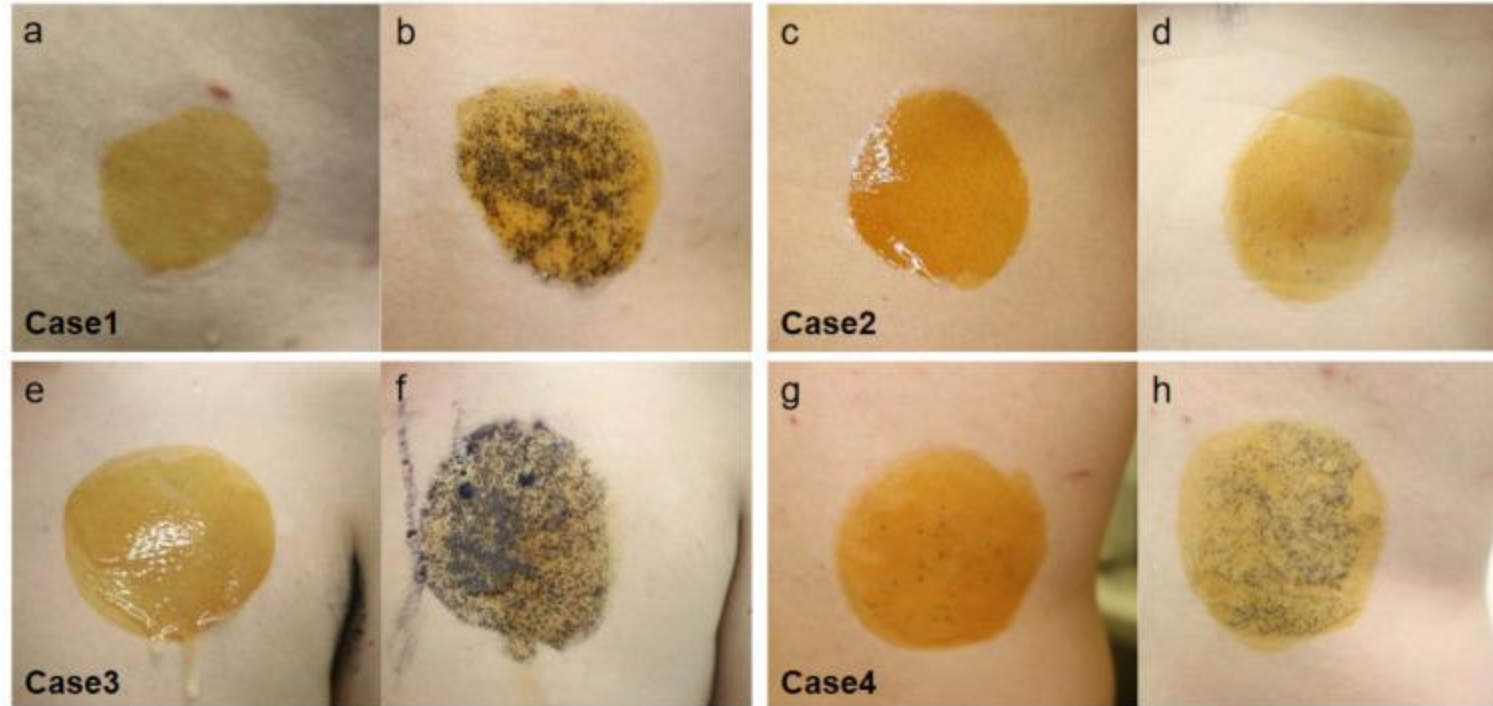
Pulse-controlled ergometry

- Moderate exercise is performed for 30 min to increase patient's heart rate by 15 beats every 5 min to a final maximum increase of 90 beats per minute above the starting level at 30 min.^[18]
- Itchy hives are considered a positive response

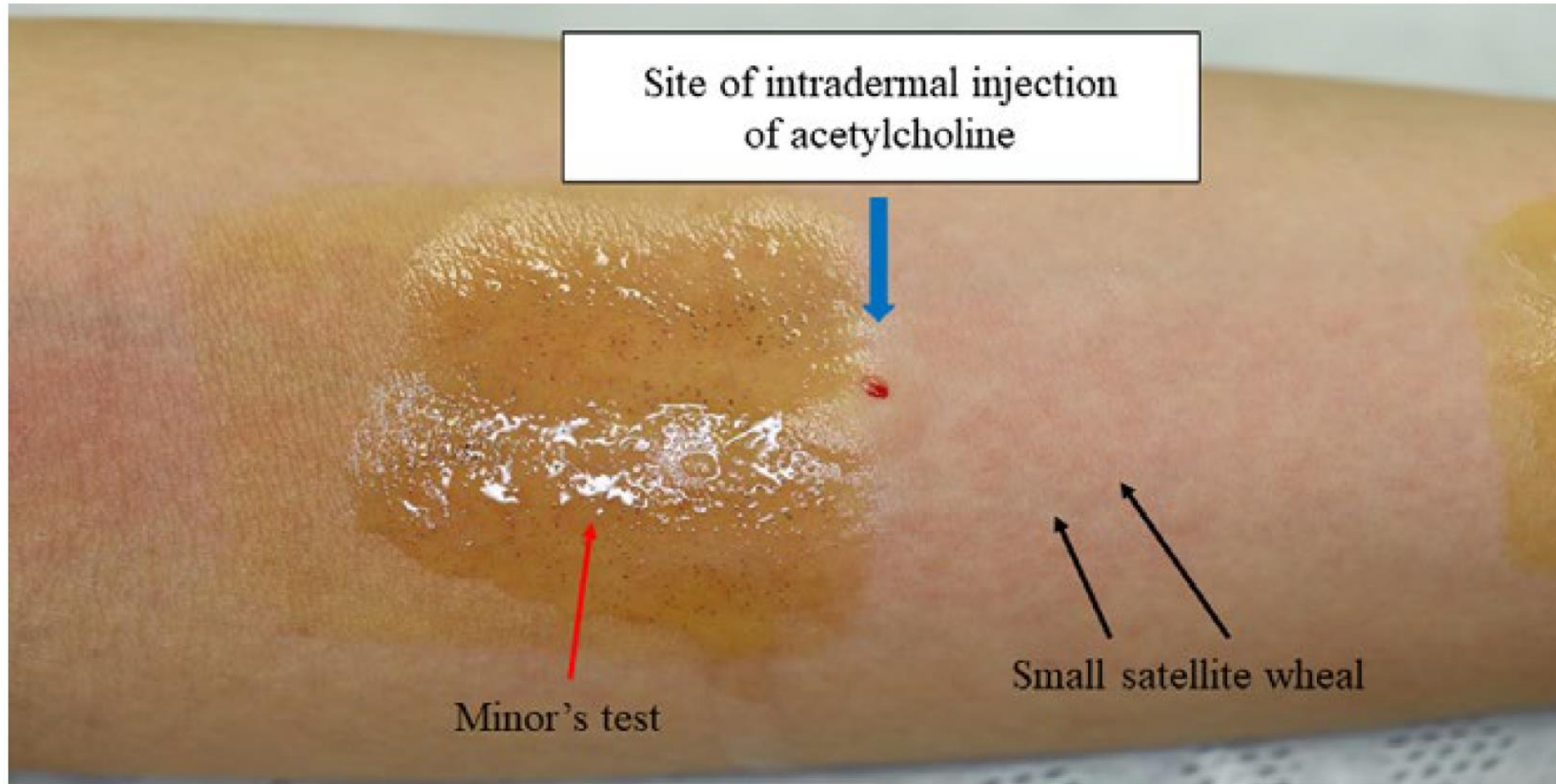
CholU Testing: Pulse-controlled Ergometry



CholU with Anhidrosis: Minor's Iodine Test



CholU: Intradermal Acetylcholine Test



Cold Urticaria (CU)

- Wheals or angioedema typically appears minutes after cold exposure
- Usually limited to exposed areas, but extensive cold exposure may trigger systemic reactions
- **Cold Urticaria Subtypes:**
 - ***Delayed cold urticaria*** - wheals occur up to 24 hours after cold exposure.
 - ***Hereditary atypical cold urticaria*** – absence of systemic inflammatory symptoms
 - ***Cold-induced cholinergic urticaria*** - hives only when exercising in cold environments.
 - ***Localized cold urticaria*** - only occurs in specific localizations (e.g., face).
 - ***Localized cold reflex urticaria*** - hives develop near the site of the ice cube challenge

Cold Provocation Testing: Ice Cube Test

- The ice cube(s) should be melting and contained within a thin plastic bag to prevent direct water contact to avoid any confusion with aquagenic urticaria if the test is positive.^[23]
- The cold stimulus is applied to the volar forearm for 5-20 min.
- Threshold testing can determine the stimulation time threshold, which is the shortest duration of cold exposure required to induce a positive test reaction.^[23]



24. Maltseva *Allergy*. 2021 Apr;76(4):1077-1094

Temperature Testing for Cold and Heat Urticaria



- This device has a single U-shaped aluminum element that generates a temperature gradient from 4°C to 44°C.^[23]
- The test area is placed on the device for 5 minutes.
- A plastic guide is used to identify the temperature threshold for wheal formation

<https://medelink.ca/allergy/sub-page-temptest/>

Temperature Test for Cold and Heat Urticaria



Solar Urticaria (SU)

- SU is a rare photodermatosis with symptoms that range from wheals/erythema to anaphylaxis.^[26]
- Urticarial lesions appear within minutes after exposure to direct sun on exposed skin.^[2,27]
- Usually resolves within minutes to hours after removal of sun exposure, rarely lasts >24h.
- Case reports of solar urticaria with fixed and delayed lesions have been described^[28]

Classic Solar Urticaria^[29]



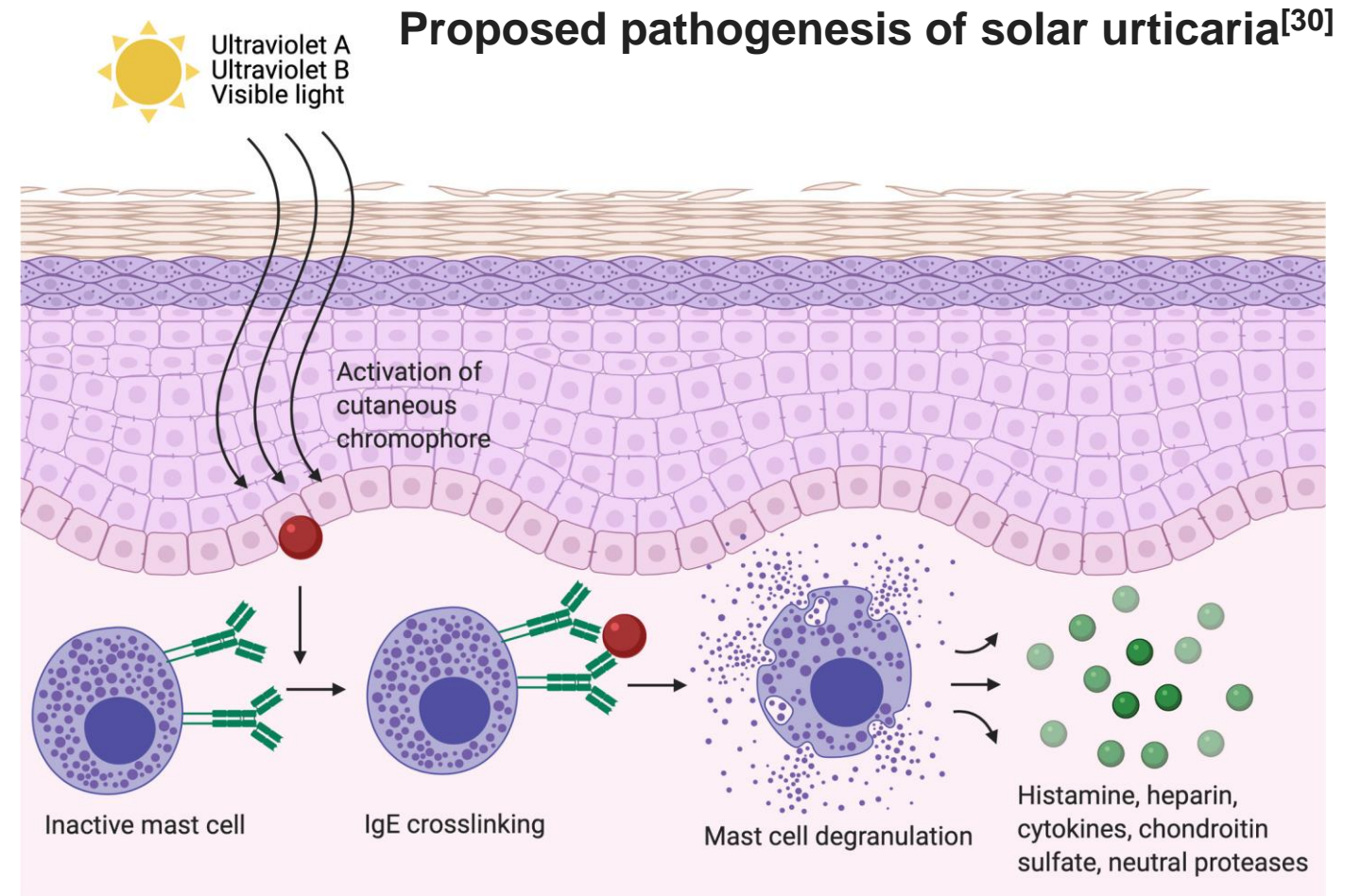
Fixed Solar Urticaria^[28]



2. Pozderac I, et al. *Acta Dermatovenerol Alp Pannonica Adriat.* 2020 Sep;29(3):141-148.
26. Oda Y, et al. *J Allergy Clin Immunol Pract.* 2020 Sep;8(8):2817-2819
27. Faurschou A, Wulf HC. *Arch Dermatol.* 2008 144 6, 765-9
28. Wessendorf U, et al. *J Am Acad Dermatol.* 2009 Apr;60(4):695-7.
29. McSweeney SM, et al. *Exp Dermatol.* 2022 Apr;31(4):586-593.

SU Pathophysiology

- A precursor molecule in the skin is activated by exposure to a particular wavelength of light and becomes a photoallergen.^[2,30, 31]
- Two possible subgroups:
 1. Specific photoallergens unique to SU patients
 2. Nonspecific photoallergens (generated in both SU and healthy patients)



2. Pozderac I, et al. *Acta Dermatovenerol Alp Pannonica Adriat.* 2020 Sep;29(3):141-148
30. McSweeney SM, et al. *Exp Dermatol.* 2022 Apr;31(4):586-593.
31. Leenutaphong V, Hölzle E, Plewig G. *J Am Acad Dermatol.* 1989 Aug;21(2 Pt 1):237-40.

SU Phototesting

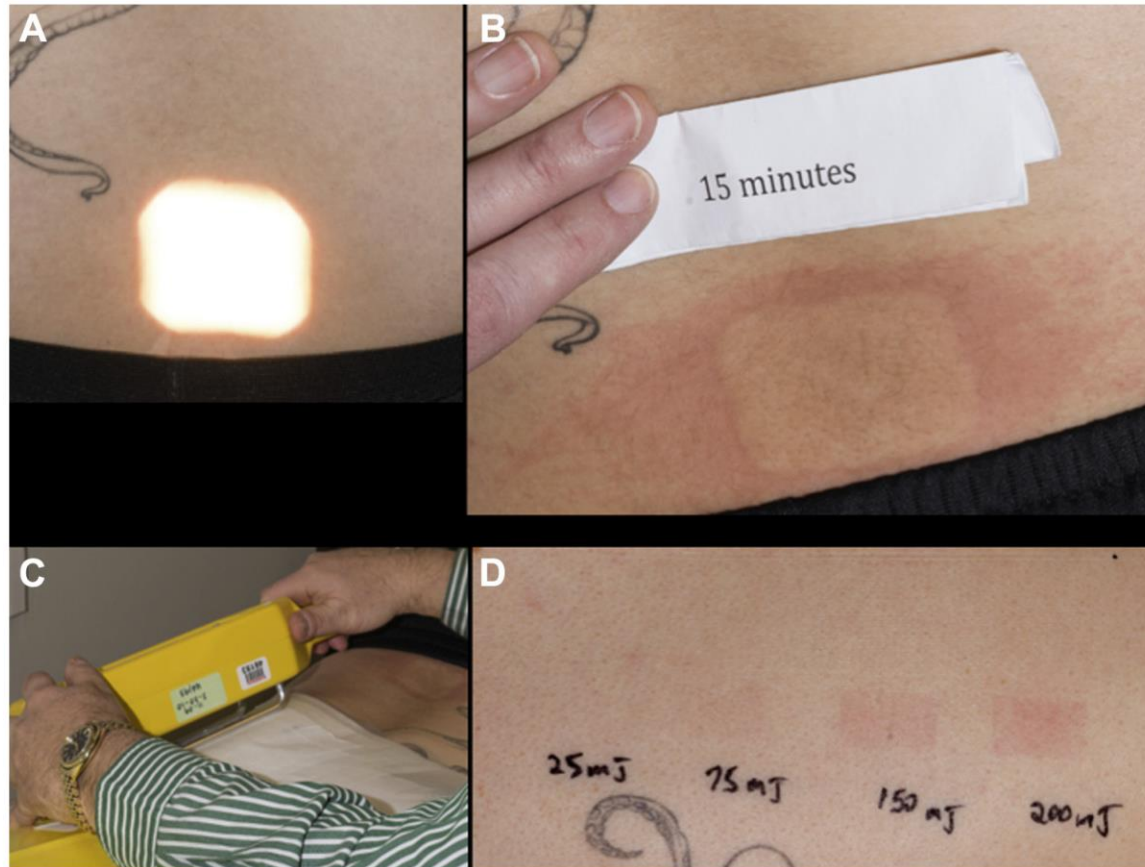
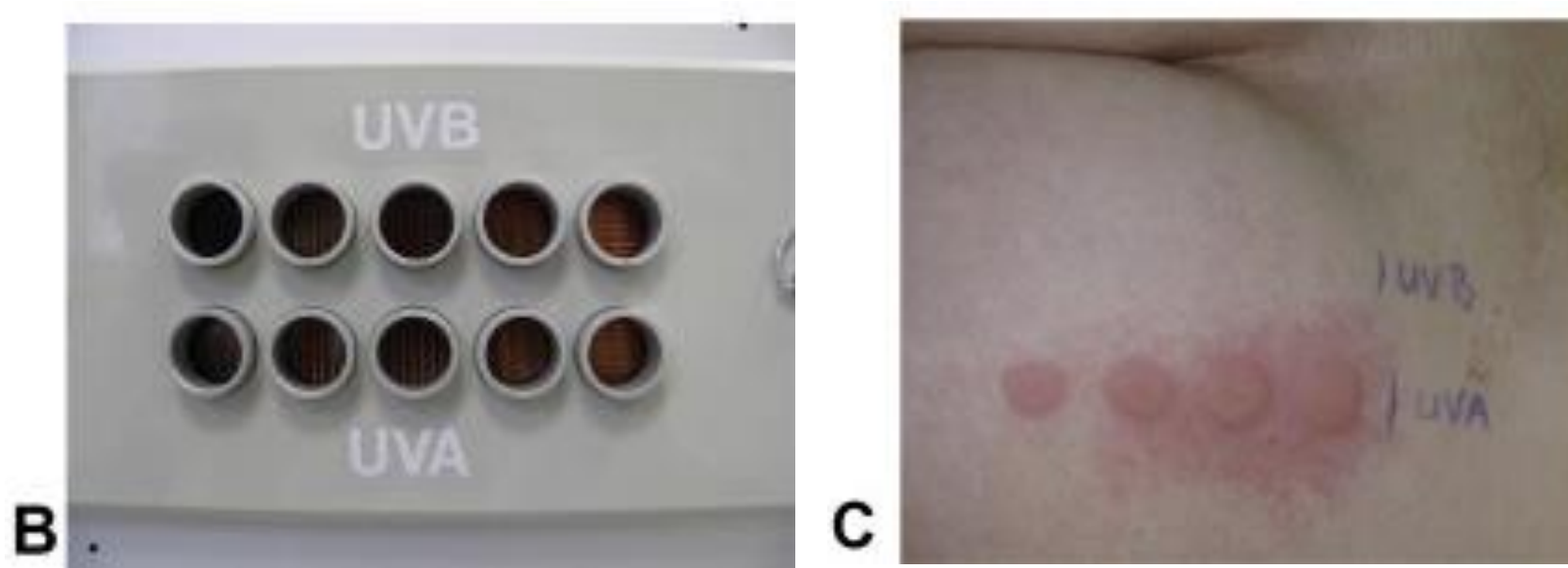


FIGURE 1. Solar urticaria challenge testing of a 27-year-old man. **A**, Visible light exposure (380-700 nm) directed to the lower back with **(B)** development of raised, erythematous wheals 15 min postexposure. **C**, UVB (290-320 nm) challenge testing and **(D)** positive urticarial reaction at 75, 150, and 200 mJ of UVB (but not at 25 mJ).

SU Phototesting



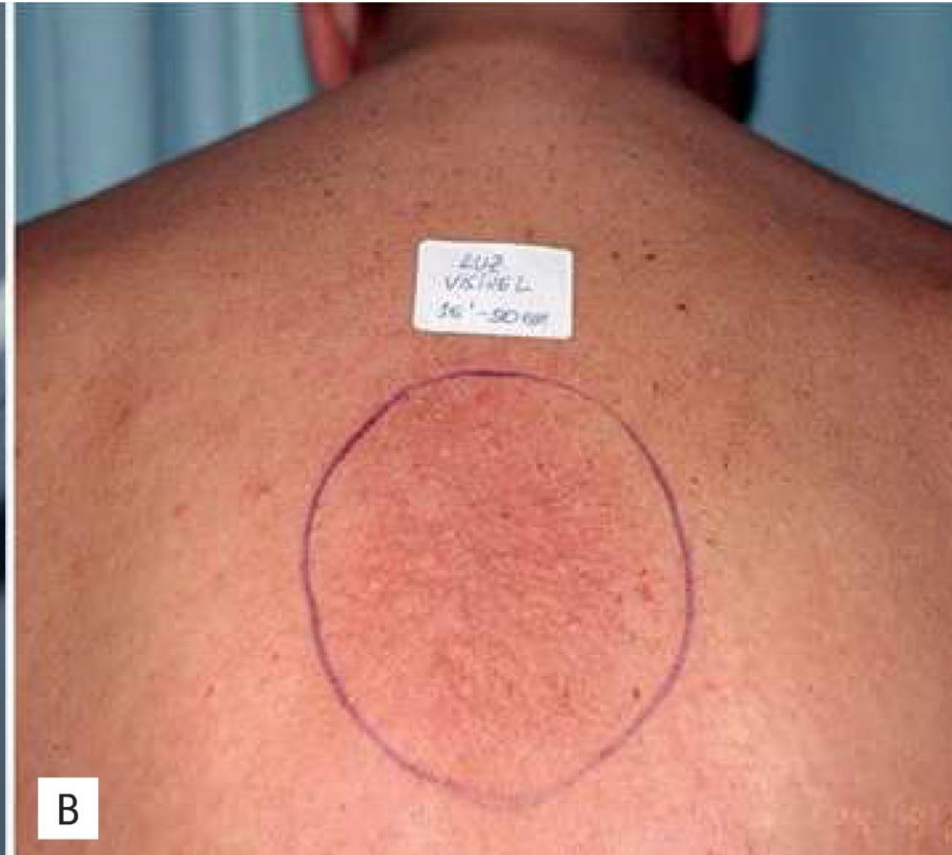
UVA+UVB Solar Simulator [16]

SU Phototesting: UV Lamp



UV radiation produced by the UV lamp is generated by a filter, which is selective for wavelengths in the UV part of the spectrum between 320 nm and 400 nm with a peak at 365 nm.

SU Phototesting: Halogen Lamp



Aquagenic Urticaria (AU)

- A rare inducible form of physical urticaria, which occurs in response to cutaneous exposure to water, including sweat and tears.^[35]
- Folliculocentric wheals appear within 20–30 min of skin contact with water.^[35,36]
- Typically resolves within 30–60 min of cessation of water contact.^[35]
- Trunk and upper arms most often affected, usually palms and soles spared.^[35]
- Affected areas are generally refractory to repeated stimulations for several hours.^[35]

35. Rothbaum R, McGee JS. *J Asthma Allergy*. 2016 Nov 29;9:209-213.

36. Shelley WB, Rawnsley HM. *JAMA*. 1964;**189**:895–898.

AU Water Provocation

- Diagnosis is based on thorough clinical history and a water provocation test.^[35]
- Standard method is to apply water at room or body temperature to a cloth and place on skin for 5-20 min.^[35,37]
- Cholinergic and heat urticaria will test negative in response to room temperature water challenge ^[35]
- Aquagenic pruritis will experience itching but no skin changes independent of temperature ^[35,38]



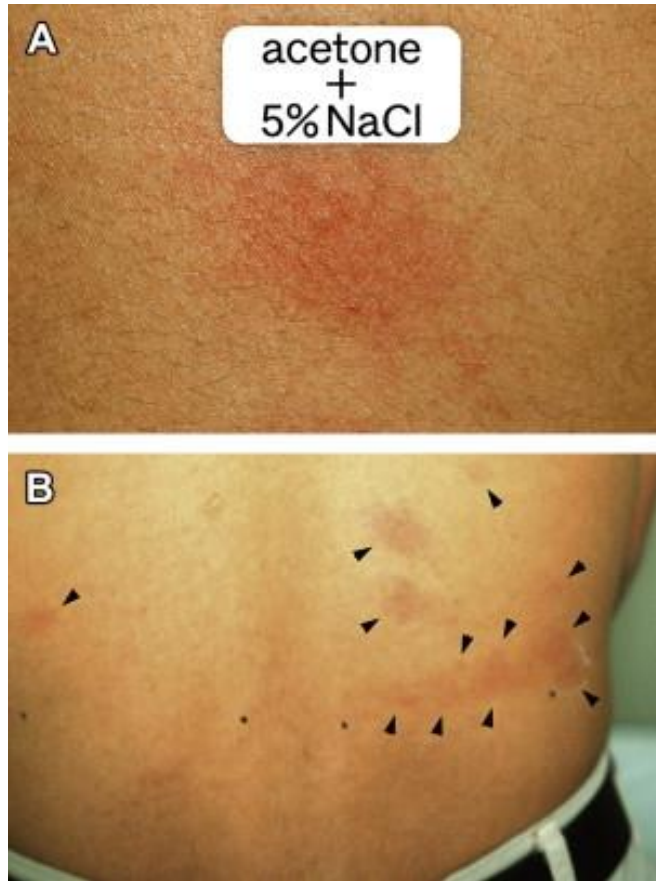
Positive test to towel soaked with body temp tap water and applied to forearm for 5 min^[38]

35. Rothbaum R, McGee JS. *J Asthma Allergy*. 2016 Nov 29;9:209-213.

37. Seol JE, et al. *Ann Dermatol*. 2017 Jun;29(3):341-345.

38. Bircher AJ, Meier-Ruge W. *Arch Dermatol*. 1988;124(1):84-89.

AU Testing with Saline and Acetone



- Wiping the test area with an organic solvent, such as acetone or ethanol, and challenging with saline instead of tap water may increase the patient's reactivity.
- In *Fig A*, a wheal and flare appeared at a hair follicle after a 15 min application of 5% saline
- In *Fig B*, more wheals appeared following pretreatment with acetone (right) vs without acetone (left)

Delayed Pressure Urticaria (DPU)

- Characterized by the development of erythematous swelling at sites of sustained pressure application on the skin after a delay of 30 min to 12 h. [40, 41]
- Lesions are usually pruritic and/or painful, can persist for days, and may occasionally blister. [40, 42]
- Systemic features such as flu-like symptoms and arthralgia may be present. [40]
- Nearly all DPU patients have associated chronic spontaneous urticaria. [40, 43]



40. Kobza-Black A. *J Investig Dermatol Symp Proc*. 2001 Nov;6(2):148-9

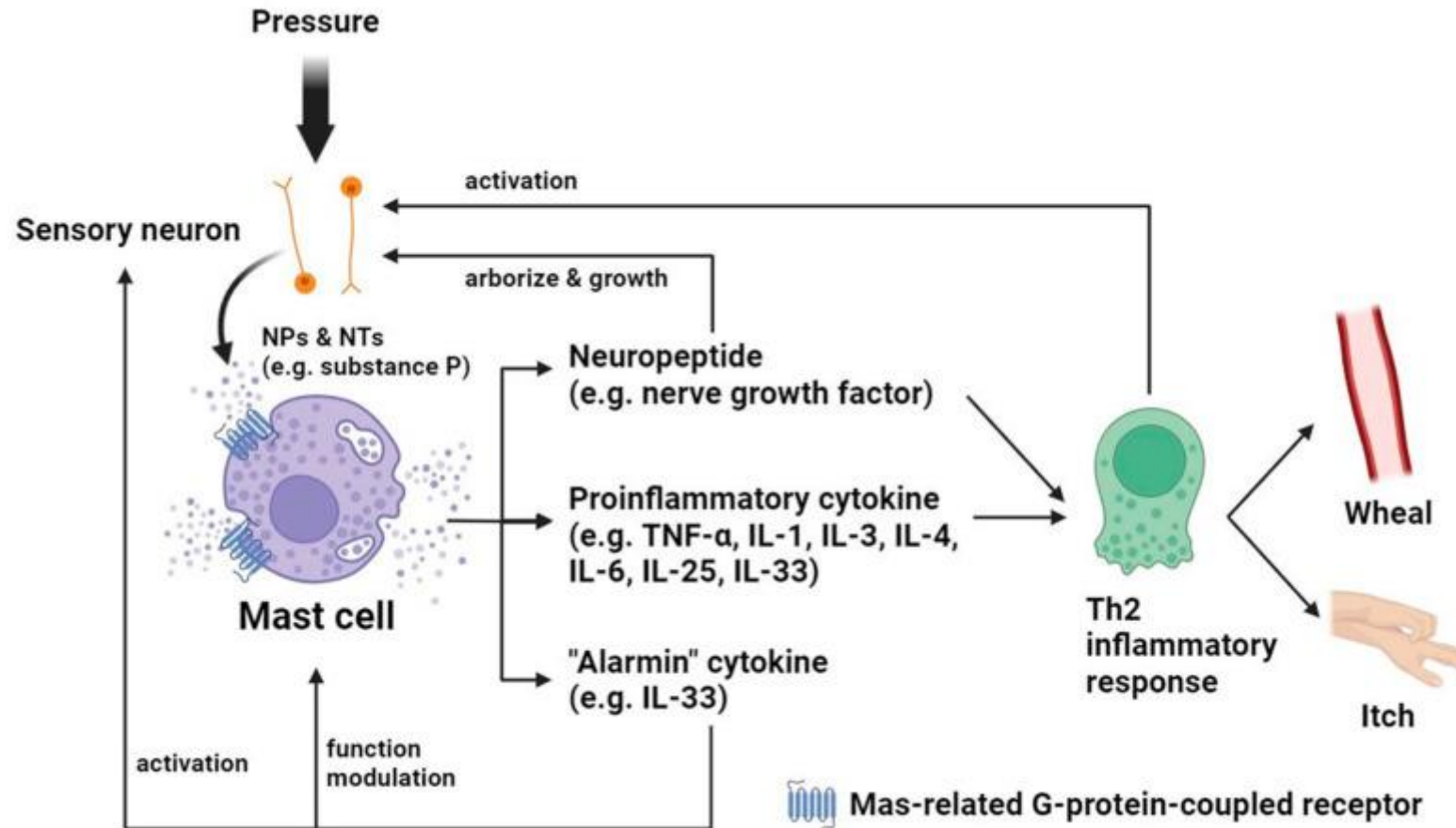
41. Dover JS, et al. *J Am Acad Dermatol*. 1988 Jun;18(6):1289-98

42. Mijailović BB, et. al. *Br J Dermatol*. 1997 Mar;136(3):434-6

43. Sussman GL, et. al. *J Allergy Clin Immunol*. 1982 Nov;70(5):337-42

44. Swerlick RA, Puar N. *Dermatol Ther*. 2015 Sep-Oct;28(5):318-22

DPU Pathophysiology



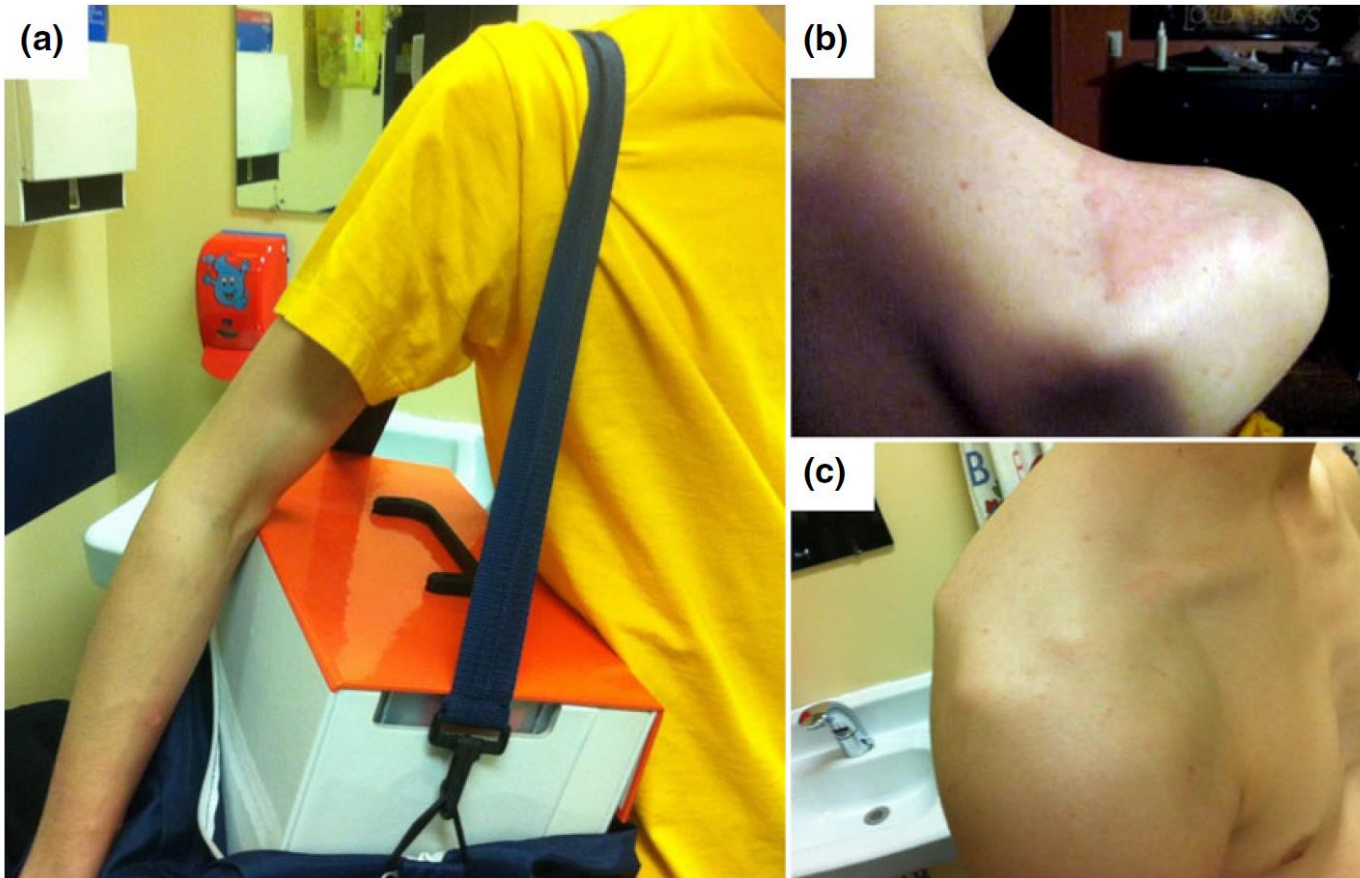
DPU Provocation Tests

- Pressure challenge test options include:
 - 2.5 or 3.5-kg rods with a 1.5-cm diameter applied for 20 minutes
 - A dermatographometer set to 100 g/mm^2 and applied for 70 seconds
 - A weight of 3–10 kg weight applied over a skin area of $2\text{--}3 \text{ cm}^2$ (usually on the thigh or shoulder) for 10–30 minutes.
- Skin assessments are performed at 4, 6, 8, 12 hours, and possibly 24 hours.



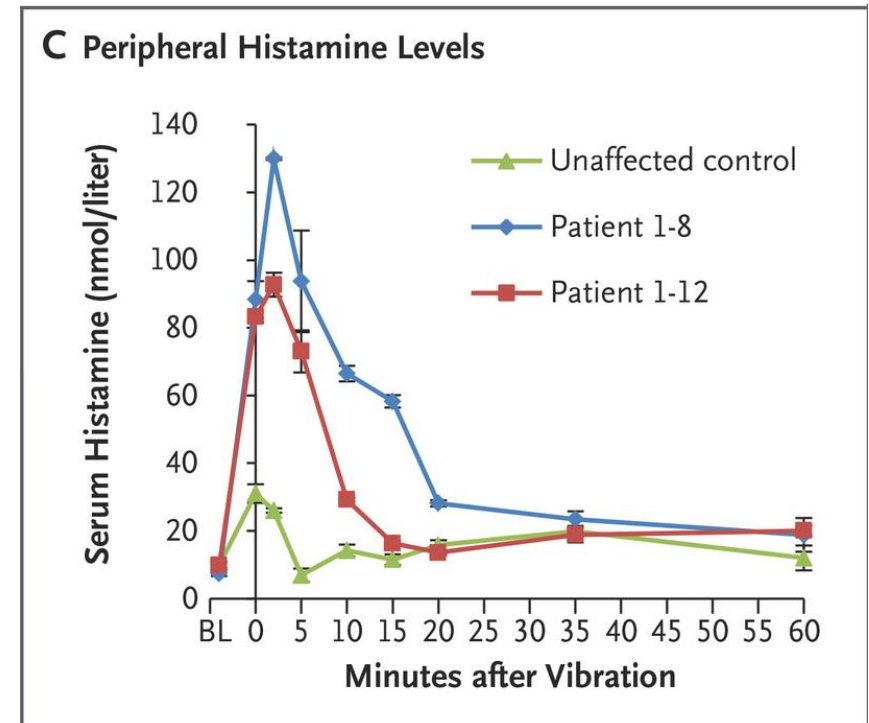
47. Morioke S, et. al. *Arch Dermatol Res.* 2010 Oct;302(8):613-7.

DPU Provocation Testing



Vibratory Urticaria (VU)

- Manifests as local swelling, or rarely wheals, several minutes to hours after using vibrating machinery, lawn mowing, applauding, and jogging.^[49]
- Symptoms peak at 4-6 hours and resolve by 24 hours ^[2]
- Systemic symptoms may occur (headache, chest tightness, diffuse flare, facial flushing). ^[49]
- Elevated serum histamine levels and mast cell degranulation (during symptomatic episodes).^[2,49,50]



2. Pozderac I, et al. *Acta Dermatovenerol Alp Pannonica Adriat.* 2020 Sep;29(3):141-148

49. Borzova E, Grattan CEH. *Cinical immunology* 6th ed. 2023;585-600.e1.

50. Boyden SE, et al. *N Engl J Med.* 2016 Feb 18;374(7):656-63.

VU Vortex Challenge

- The volar surface of the forearm or hand is placed on the vortex mixer.^[51-53]
- If using a fixed speed mixer, run at 2500rpm for 4-5 min ^[52]
- If using a variable speed mixer, can run at a lower speed (780–1380rpm) for 10 min ^[51]
- Measure the circumference of the forearm at 3 points (cubital fossa, wrist, and midpoint between the two) before and 5 min after the challenge ^[51-53]
- The result is considered positive if inflammation is induced ^[54]

51. Hide M, Hiragun M, Hiragun T. *Immunol Allergy Clin North Am*. 2014 Feb;34(1):53-72.

52. Borzova E, Grattan CEH. *Cinical immunology* 6th ed. 2023;585-600.e1.

53. Boyden SE, et al. *N Engl J Med*. 2016 Feb 18;374(7):656-63.

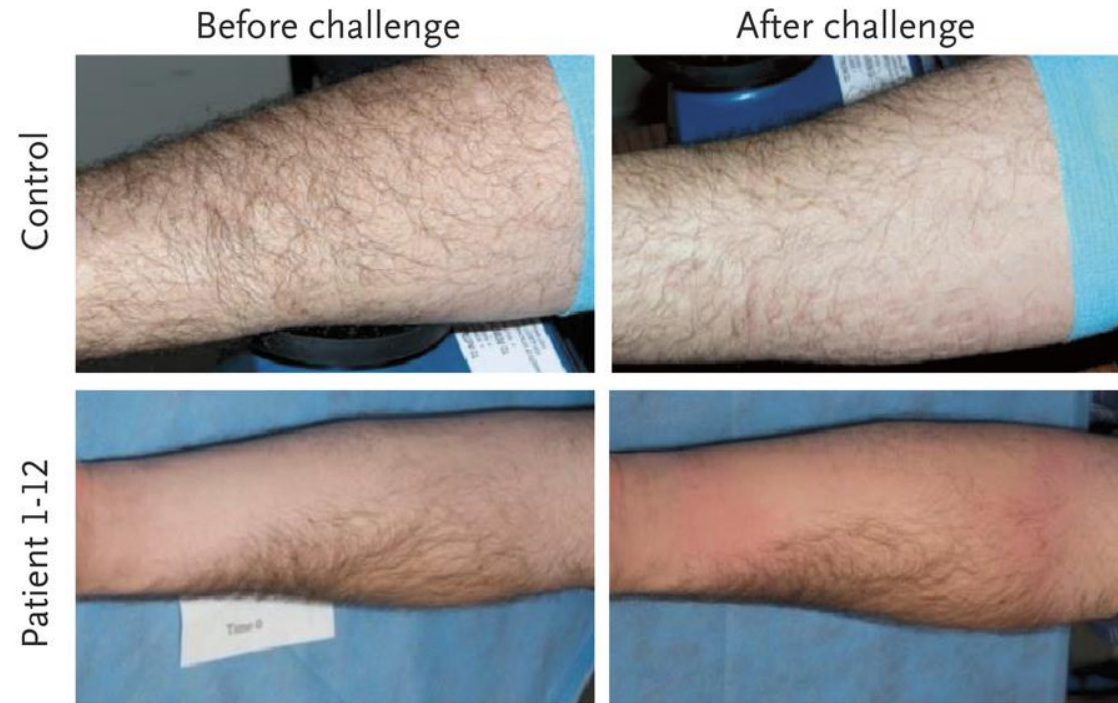
54. Pastor-Nieto MA. *Actas Dermosifiliogr*. 2022 Oct;113(9):T900-T904



Variable Speed Vortex Mixer^[51]

VU Vortex Challenge (Forearm)

B Forearm Vortex Challenge



53. Boyden SE, et al. *N Engl J Med.* 2016 Feb 18;374(7):656-63.

VU Vortex Challenge (Hand)

A



0



5



15



30

The time after provocation (minutes)

Podium to Practice Takeaways

- A thorough history is the most important aspect of diagnosing chronic inducible urticaria.
- If provocative testing is positive for one condition, ensure that the test procedure did not trigger a false positive.
- If initial provocative testing is negative, consider repeating test under “real world” conditions.