

How to Approach Chronic Inducible Urticaria



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List of Design Committee Members: Marcus Maurer, MD, Joachim W. Fluhr, MD, and David A. Khan, MD (authors); Michael Schatz, MD, MS (editor)

Learning objectives:

1. To describe new insights into the pathomechanisms of chronic inducible urticaria (CIndU).
2. To describe the currently available tools for provocation and threshold testing of the different CIndUs.
3. To recognize the therapeutic and prophylactic options in different CIndUs.

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Chronic inducible urticaria (CIndU) is a group of chronic urticarias characterized by the appearance of recurrent wheals, recurrent angioedema or both, as a response to specific triggers. CIndU includes both physical (symptomatic dermographism, cold and heat urticaria, delayed pressure urticaria, solar urticaria, and vibratory urticaria) and nonphysical urticarias (cholinergic urticaria, contact and aquagenic urticaria). Here, we review the

different forms of CIndU with an emphasis on symptomatic dermographism, cold urticaria, cholinergic urticaria, and delayed pressure urticaria. We discuss the clinical features, the diagnostic workup including provocation and threshold testing, and available treatment options. © 2018 American Academy of Allergy, Asthma & Immunology (*J Allergy Clin Immunol Pract* 2018;6:1119-30)

Key words: Chronic inducible urticaria; Cold urticaria; Symptomatic dermographism; Cholinergic urticaria; TempTest

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Chronic inducible urticaria (CIndU) is a subgroup of chronic urticaria (CU) where recurrent pruritic wheals and/or angioedema occur after exposure to specific stimuli. CIndU includes both physical (symptomatic dermographism [SD], cold and heat urticaria, delayed pressure urticaria [DPU], solar urticaria, and vibratory urticaria) and nonphysical urticarias (cholinergic urticaria [CholU], contact and aquagenic urticaria; Table 1). CIndU is common, with an estimated prevalence of 0.5%, and many patients are severely disabled, mainly due to the impact of trigger avoidance. In adults, there is a female predominance for the total group of physical urticarias (74% female).^{1,2}

CIndU has several differences compared with chronic spontaneous urticaria (CSU). The duration of CIndU is often longer

Abbreviations used*CholU*-Cholinergic urticaria*CIndU*-Chronic inducible urticaria*ColdU*-Cold urticaria*CSU*-Chronic spontaneous urticaria*CU*-Chronic urticaria*DPU*-Delayed pressure urticaria*FACU*-Familial atypical cold urticaria*FCAS*-Familial cold autoinflammatory syndrome*PLAID*-Phospholipase C- γ 2-associated deficiency and immune dysregulation*QoL*-Quality of life*SD*-Symptomatic dermographism*TRP*-Transient receptor potential

than CSU, with lower rates of remission at 1 year and some studies showing the lowest rate of remission after 10 years for cold urticaria (ColdU).^{3,4} The duration of individual wheals is often relatively brief for CIndU, lasting minutes to hours, with the exception being DPU. In addition, systemic symptoms of mast cell activation may occur in many types of CIndU. A large portion of patients with ColdU and CholU (35% to 70%) experience systemic reactions including anaphylaxis, after extensive cold exposure and exercise, respectively.⁵⁻⁷

CIndUs are diagnosed based on the patient history and the results of provocation tests, which make use of the relevant stimuli in controlled settings. ColdU, for example, is confirmed by applying cold (eg, an ice cube) to the skin of patients, SD is tested by scratching of the skin, and exercise and passive warming (eg, a warm bath) are used for CholU provocation testing. Disease activity, in patients with CIndU, is assessed by threshold testing and activity scores, where available.

The therapeutic goal of CIndU management is to achieve complete symptom control, by trigger avoidance, desensitization, blocking the effects of mast cell mediators (eg, by nonsedating, second-generation antihistamines), and prevention of mast cell degranulation.

PATHOPHYSIOLOGY OF CIndU

The exact pathological mechanisms that result in CIndU are still under investigation. The activation and degranulation of tissue-resident mast cells and the subsequent release of proinflammatory mediators such as histamine play key roles.⁸⁻¹¹ The efficacy of anti-IgE (omalizumab) in many patients with CIndU points to a possible role of IgE in the degranulation of mast cells in CIndU. Type I autoimmunity, also known as autoallergy, is held by many to be of major importance in the pathogenesis of CIndU. The hypothesis is that different autoantigens bind to IgE on skin mast cells and basophils activating these cells.¹² Relevant environmental triggers are thought to induce *de novo* expression of these autoallergens. The autoallergens then bind to IgE (specific for these autoallergens) bound to Fc ϵ RI on skin mast cells, inducing their degranulation.¹²⁻¹⁴ In support of this concept, patients with CIndU express increased serum levels of total IgE.¹³ In several subtypes of CIndU, for example, SD, ColdU, and solar urticaria, the disease is passively transferable by transfer of serum, with IgE being the suggested transferable serum factor.^{15,16} In solar urticaria, specific photo-induced autoantigens have been suggested to bind to IgE on mast cells.^{17,18} An older study in ColdU showed desensitization by depletion of a cold-dependent

skin antigen that can activate mast cells.¹⁹ These studies support the concept that IgE binding to Fc ϵ RI on skin mast cells may be important in the pathogenesis of CIndU, explaining the responsiveness of CIndU to anti-IgE treatment.²⁰⁻²²

Mast cells and basophils may also be activated through IgE-independent pathways. An area of recent research in physical urticaria has been the role of transient receptor potential (TRP) channels that can be regulated by changes in temperature, pH, or osmolality and produce calcium influx into the cells. Studies using a rat basophilic leukemia cell line suggested that the transient receptor potential cation channel subfamily M member 8 (TRPM8) channel was activated on exposure to cold temperatures with mediator release.²³ However, subsequent studies of human mast cells found no expression of TRPM8 or functional mutations in TRPM8 in patients with ColdU.²⁴ The role of other TRP proteins in CIndU is unknown.

It has been reported that CIndU and CSU are associated in some patients, especially in physical urticaria and have a worse prognosis. Exact data are not available on the prevalence of CIndU and CSU.^{25,26}

Our following review is focused on the 4 most frequent types of CIndU: SD, ColdU, CholU, and DPU.

SYMPTOMATIC DERMOGRAPHISM

Clinical features

SD (synonym: urticaria factitia, dermographic urticaria) is the most common physical urticaria and characterized by itching and/or burning skin sensations and the development of itchy wheals in response to rubbing, scratching, and/or scrubbing, that is, shearing forces acting on the skin. In very rare cases, angioedema can develop. SD is clinically distinct from the more common "simple" dermographism, where whealing, but no itch sensation, occurs after firm stroking of the skin. White dermographism (as seen in atopic patients) is not related to SD.

SD is often linked to CSU. In a group of 245 patients with CSU, SD was the most common type of CIndU, affecting 25% of the CSU group.²⁶ In a retrospective study of 1200 patients with CSU, SD was the most prominent form of CIndU.¹

SD is chronic and usually of duration of several years before spontaneous remission. In a questionnaire survey of 91 patients with SD, the mean duration of disease was 6 $\frac{1}{4}$ years.²⁷⁻²⁹ In most patients, the condition was continuous, and 25% had prolonged symptom-free phases.

The symptom severity of SD was evaluated in 150 patients and found to be mild in 17%, moderate in 45%, severe in 33%, and very severe in 6% of patients.² Quality of life (QoL) was significantly impaired in 42% of patients, and 7% stated that a normal life was not possible for them. These patients reported being affected with fatigue (62%), sleep disturbance (53%), both during work (60%), or leisure (61%).² In 27 patients with SD, 43% reported that their disease had an impact on their QoL. One in 3 patients report that psychosocial stress amplifies the symptoms.³⁰

Diagnostic workup

Many patients with SD can be identified through the history. Patients with CU who report pruritus without visible rash, followed by linear wheals that last minutes, should be evaluated for SD. Many patients describe chronic itch or a "skin crawling" sensation leading to scratching. A review of patient photographs for linear wheals can also assist in the diagnosis.

TABLE I. Subtypes of CIndUs: definitions and estimated prevalence

Subtype of CIndU	Trigger	Prevalence among patients with CIndUs
Physical urticaria		
Symptomatic dermographism (also called urticaria factitia)	Shear force acting on the skin (ie, friction)	Adults: 50% to 78%, children: 38%
Cold urticaria (also called cold contact urticaria)	Cold exposure to the skin	Varies by climate. Adults: 8% to 37%, children: 9% to 14%
Delayed pressure urticaria	Application of sustained pressure to the skin	Adults: 3% to 20%, children: 3% to 9%
Solar urticaria	Light (UV and/or visible light) exposure	Very rare; limited data
Heat contact urticaria	Heat exposure of the skin	Very rare; limited data
Vibratory angioedema	Exposure to vibration	Very rare; limited data
Other inducible urticaria		
Cholinergic (including exercise induced)	Active or passive body warming	Adults: 6% to 13%, children: 19%
Contact urticaria	Contact with eliciting agent	Very rare; limited data
Aquagenic urticaria	Skin contact with water	Very rare; limited data

CIndU, Chronic inducible urticaria; UV, ultraviolet.

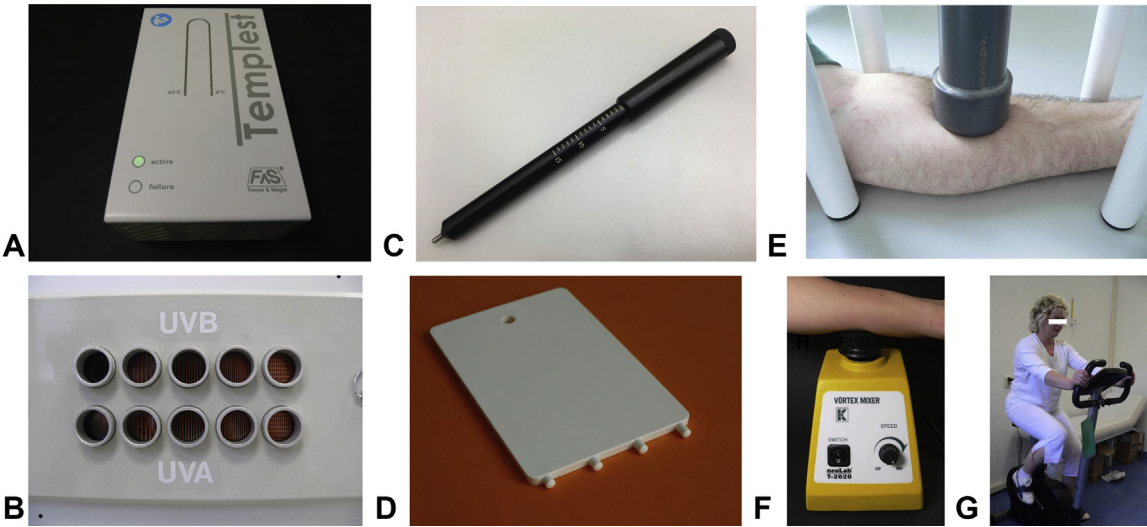


FIGURE 1. Testing instruments for CIndUs. **A**, TempTest 4.0 for provocation and threshold testing in cold urticaria. **B**, UVA- and UVB-simulator for provocation and threshold testing in solar urticaria. **C**, HTZ dermographometer for provocation and threshold testing in symptomatic dermographism. **D**, FricTest for provocation and threshold testing in symptomatic dermographism. **E**, Pressure device to be loaded with different weight for provocation and threshold testing in delayed pressure urticaria. **F**, Standard laboratory vortex device for provocation and threshold testing in vibratory angioedema. **G**, Bicycle ergometer for standardized provocation and threshold testing in cholinergic urticaria. CIndU, Chronic inducible urticaria; UV, ultraviolet.

After a careful medical history including comorbidities, the diagnosis of SD should be assessed through provocation testing. Most commonly, this is performed by using a wooden tongue blade and applying firm pressure in a stroking motion to the skin. Commercially available calibrated dermographometers provide a more uniform method of testing using a specific tool with defined pressure settings. The skin test site should be free of signs of infection or inflammation. A wheal response without itch indicates simple dermographism seen as a physiological variation. A response is considered positive if a pruritic palpable wheal is present within 10 minutes of provocation.

A calibrated dermographometer is commercially available (HTZ Limited, London, UK) (Figure 1, C). It has a spring-

loaded smooth steel tip of 2.3 mm in diameter. The scale settings from 0 to 15 are equivalent to a range of tip pressures from approximately 20 to 160 g/mm² (196-1569 kPa). The induction of a pruritic and palpable wheal to the applied pressure of <36 g/mm² is considered as positive for SD. The tool's adjustability allows for determining the patient's trigger threshold. Provocation and threshold testing can also be performed with FricTest, a dermographic tester (Moxie, Berlin, Germany) in the shape of a plastic comb with 4 tips (which are 3.0, 3.5, 4.0, and 4.5 mm in length, respectively), which apply graded shearing forces to the skin (Figure 1, D). Each tip is 3 mm in diameter and has a slightly rounded end to minimize skin surface impairment. To obtain a response, the instrument is placed vertically so that the

TABLE II. Classification of cold urticaria syndromes

Type of cold urticaria	Immediate cold provocation test	Comments
Acquired cold urticaria		
Primary	Positive	Most common, idiopathic
Secondary		
Cryoglobulinemia	Positive	Cryoglobulins and decreased CH50
Leukocytoclastic vasculitis	Positive	Skin biopsy with leukocytoclastic vasculitis and decreased CH50
Infectious diseases	Positive	Positive infectious serology (eg, rapid plasma reagin, Epstein-Barr virus antibodies)
Atypical acquired cold urticaria		
Systemic atypical acquired cold urticaria	Negative	Localized or generalized urticaria with cold exposure
Cold-dependent dermographism	Negative	Dermographic whealing after stroking precooled skin
Cold-induced cholinergic urticaria	Negative	Exercise in cold environments leads to generalized urticaria
Delayed cold urticaria	Negative	Urticaria develops 12-48 h after application of cold provocation
Localized cold reflex urticaria	Negative	Positive immediate urticarial response at a site distant to cold provocation
Hereditary cold urticaria syndromes		
Familial cold autoinflammatory syndrome	Negative	Pseudourticaria, fever, arthralgia, conjunctivitis occurring 1-2 h after cold exposure Autosomal dominant disorder due to mutation in <i>NLRP3</i>
Phospholipase C- γ 2-associated deficiency and immune dysregulation	Negative	Cold urticaria onset at young age, antibody deficiency, autoimmunity Positive tests for evaporative cooling

tips are touching the skin, and then stroked once across the width of the volar surface for a distance of approximately 60 mm. A response to demographic testing is considered positive if a pruritic palpable wheal of ≥ 3 mm width is present within 10 minutes after provocation.

Treatment

All patients with SD should be educated about the importance of trigger avoidance. In addition, patients should be advised to use, daily, a nonsedating second-generation H1 antihistamine at the licensed dose as first-line therapy. Patients who do not obtain complete control with this treatment should be advised to increase the dose of their antihistamine up to 4 times the standard dose.^{4,31-33} In the aforementioned study by Schoepke et al,² antihistamine therapy resulted in complete control of symptoms in 23% of patients, marked improvement in 49% with only 4% reporting no effect. H2 antagonists along with H1 antihistamines have been reported to improve SD in some small studies.³⁴⁻³⁶ Treatments recommended for antihistamine-resistant patients are omalizumab^{33,37,38} and cyclosporine. Phototherapy and photochemotherapy have also been reported to be effective but are less frequently used.³⁹⁻⁴² Omalizumab resulted in a high rate of complete and partial responders in 55 patients with SD and a pronounced overall reduction in disease activity.²¹ This study showed that patients with SD unresponsive to antihistamine treatment benefit from treatment with omalizumab.

COLD URTICARIA

Clinical features

ColdU (synonym: acquired ColdU or cold contact urticaria) is characterized by the appearance of wheals after contact with cold or cooling and rewarming of the skin (Table II).⁴³⁻⁴⁶ ColdU is the second most frequent subtype of physical urticaria. The

annual incidence is 0.05%⁴⁷ with predominant manifestation in young adults and slightly higher prevalence in women.⁶ The clinical symptoms occur within minutes after skin contact with cold air, cold liquids, cold solid objects, or evaporation-based cooling and persist for approximately 1 hour.^{37,44,48} In severe cases, patients can develop systemic involvement including anaphylaxis.⁴⁹ Local angioedema affecting the lips, tongue, or pharyngeal tract has been associated with shock like reactions after swimming in cold water.⁵ The disease duration of ColdU is reported between 4.8 years and 7.9 years.^{6,7,47}

Cold urticarias can be classified as those with typical responses to cold provocation tests, those with atypical responses to cold provocation, and those with familial forms⁵⁰ (Table III).

Primary acquired ColdU is the most common form of ColdU and is considered idiopathic in nature. Secondary acquired ColdU is very rare and associated with an underlying disease most commonly cryoglobulinemia, but infectious causes, leukocytoclastic vasculitis, and some drug-induced cases have been reported. Both primary and secondary acquired ColdU have typical positive responses to cold provocation.

Several other rare forms of atypical acquired ColdU exist, which have negative immediate tests to cold provocation and include systemic atypical acquired ColdU, cold-dependent dermographism, cold-induced CholU, delayed ColdU, and localized cold-reflex urticaria.

Lastly, 3 hereditary forms of ColdU have been described. Familial cold autoinflammatory syndrome (FCAS), previously known as familial cold urticaria, is characterized by early onset of an urticarial rash that occurs 1 to 2 hours after cold exposure and is associated with systemic symptoms of fever, arthralgia, conjunctivitis, and leukocytosis. Immediate cold provocation tests are negative in these patients. FCAS is caused by mutations in *NLRP3* (cryopyrin) and is inherited in an autosomal dominant

TABLE III. Availability of tests, activity scores, and patient-related outcome parameter tools for CIndUs

	Provocation testing protocols	Threshold testing protocols	Disease activity scores	QoL questionnaire	Control test	Severity index	Biomarker for disease activity
Symptomatic dermatographism	+ ⁹⁰	+ ⁹⁰	—	Under development	+ ^{127,128}	—	—
Cold urticaria	+ ⁹⁰	+ ⁹⁰	—	Under development	+ ^{127,128}	+ ⁵⁸	—
Heat urticaria	+ ⁹⁰	+ ⁹⁰	—	—	+ ^{127,128}	—	—
Solar urticaria	+ ⁹⁰	+ ⁹⁰	—	—	+ ^{127,128}	—	—
Delayed pressure urticaria	+ ⁹⁰	+ ⁹⁰	—	—	+ ^{127,128}	—	—
Vibratory angioedema	+ ⁹⁰	—	—	—	+ ^{127,128}	—	—
Cholinergic urticaria	+ ⁹⁰	+ ⁹⁴	+ ⁹⁸	+ ⁹⁵	+ ^{127,128}	+ ⁹⁴	—
Contact urticaria	+ ⁹⁰	—	—	—	+ ^{127,128}	—	—
Aquagenic urticaria	+ ⁹⁰	—	—	—	+ ^{127,128}	—	—

CIndU, Chronic inducible urticaria; QoL, quality of life.

fashion.⁵¹ FCAS is the mildest form of cryopyrin-associated periodic syndromes, which also include Muckle-Wells syndrome and neonatal-onset multisystem inflammatory disease.⁵²

Familial atypical cold urticaria (FACU) is inherited in an autosomal dominant fashion and is characterized by cold-induced pruritus, urticaria, angioedema, and sometimes syncope with direct contact with a cold environment or object.⁵³ Symptoms typically begin early in childhood (6 months to 4 years), are lifelong, and occur rapidly with cold exposure/contact. Subsequent studies have identified that most of these patients with FACU have been identified as having phospholipase C- γ 2-associated deficiency and immune dysregulation (PLAID).⁵⁴ This is an autosomal dominantly inherited condition characterized by ColdU at a young age, antibody deficiency, and autoimmunity. All of these patients have negative skin tests for cold provocation but will react to evaporative cooling. Whether FACU and PLAID are the same syndrome is not entirely clear, and not all patients have autoimmunity or antibody deficiency.

Diagnostic workup

Provocation tests should be performed by applying a defined cold stimulus to the surface of the volar forearm. Traditionally, testing is performed with an ice cube, cool packs, or cold water baths. Testing with cool packs or cold water baths carries the risk of systemic reactions and should not be performed. Testing with an ice cube should be performed with the ice cube placed within a thin plastic bag together with some water to avoid cold damage and to prevent direct water contact, which can result in false positive reactions in patients with aquagenic urticaria.⁵⁵

Standardized temperature exposure tests can be performed with TempTest (Courage & Khazaka, Cologne, Germany) (Figure 1, A). TempTest is a Peltier element-based temperature exposure device. The TempTest 4.0 model has a single Peltier element (length: 350 mm, width: 2 mm) that provides a continuous temperature gradient from 4°C to 44°C.⁵⁶ The use of TempTest allows for reproducible and standardized cold (and heat) provocation tests and the identification of temperature and stimulation thresholds.^{56,57}

Cold provocation testing should be performed for 5 minutes. In some patients, shorter or longer provocation times may be appropriate. Test sites should be inspected and the responses be assessed 10 minutes after the end of provocation testing. The test should be considered positive if the test site shows a palpable and clearly visible wheal and flare-type skin reaction associated, in

most cases, with itch and/or a burning sensation. In patients who show a positive test reaction, threshold testing should be performed if possible.

Threshold testing is carried out to determine the stimulation time threshold or the temperature threshold. The stimulation time threshold⁷ is the shortest duration of cold exposure sufficient to induce a positive test reaction. Stimulation time thresholds are determined by reducing, in 1-minute decrements, the time of cold application. Stimulation time threshold tests can be carried out with an ice cube or TempTest. Ice cube stimulation time thresholds of ≤ 3 minutes are associated with higher disease activity.⁷ The temperature threshold of patients with ColdU, that is, the highest temperature sufficient to induce a positive test reaction, can be assessed with TempTest, but not by ice cube testing. Temperature thresholds should be determined whenever TempTest is available, as this information can help patients to avoid risky situations in their daily lives. Temperature threshold measurements are useful for assessing disease severity and activity as well as the efficacy of therapy.⁵⁸

Patients with PLAID have negative immediate cold provocation tests. Evaporative cooling tests can be performed with 0.5 mL droplets of water alone, water covered by the environment, water with air flow, and ethanol for 10 minutes. Positive tests include erythema, swelling, and pruritus of the site.

Treatment

All patients should be advised to avoid prolonged skin contact with cold objects or exposure to air temperatures that are below their threshold temperature. The first-line symptomatic treatment are nonsedating H1 antihistamines.⁵⁹⁻⁶² The standard antihistamine dose does not provide complete protection in all patients. Updosing of H1 antihistamines is effective in patients with ColdU who do not respond to standard doses.⁶³⁻⁶⁷ Antihistamine-resistant ColdU patient can benefit from omalizumab treatment,^{38,68-70} antibiotic treatment,⁷¹ and cold desensitization.^{14,72} Because anaphylaxis with systemic cold exposure (eg, swimming in cold water) may occur in a subset of patients, prescribing epinephrine autoinjectors may be appropriate. The authors do not routinely prescribe epinephrine to all patients with ColdU but those with prior histories of cold-induced anaphylaxis and those with histories of angioedema affecting the lips, tongue, or pharyngeal tract are at high risk and should be counseled and prescribed epinephrine autoinjectors.

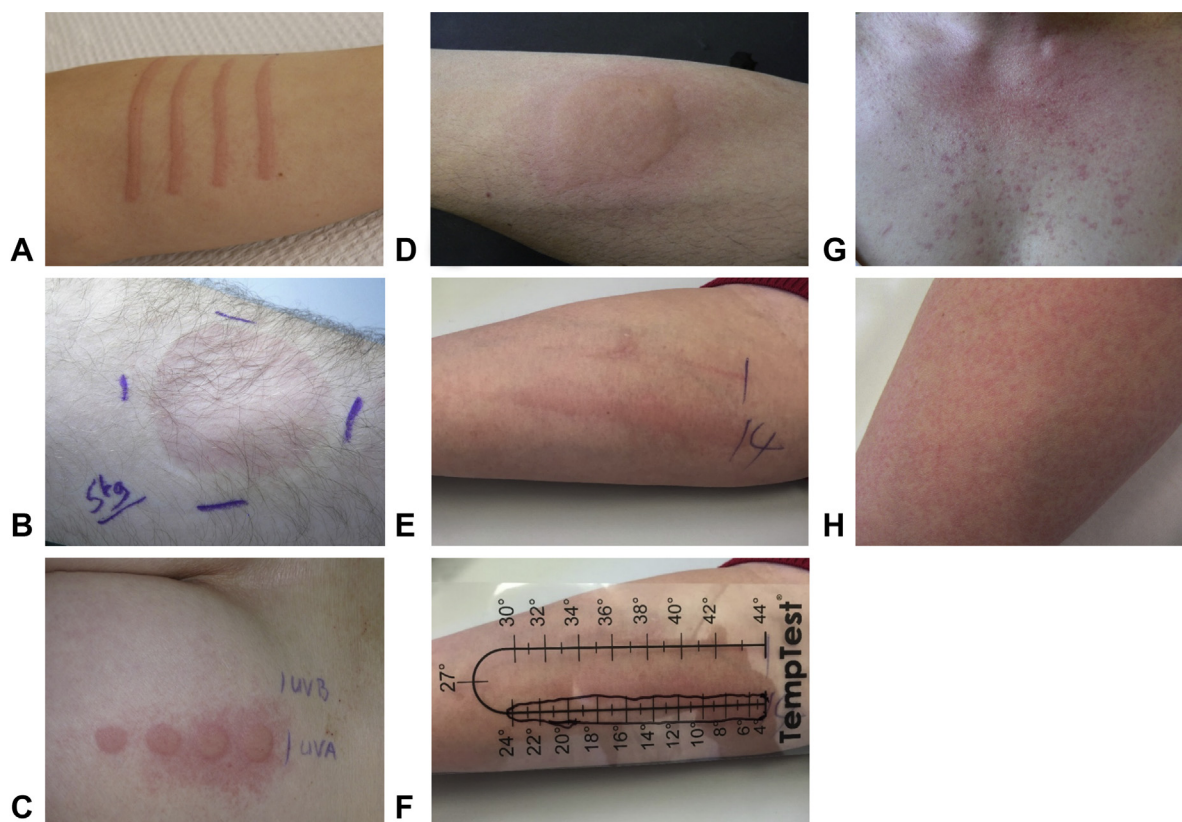


FIGURE 2. Clinical features of different CIndUs. **A**, Symptographic dermatographism. **B**, Delayed pressure urticaria. **C**, UV-induced urticaria. **D**, Cold urticaria (induced with ice cubes). **E**, Cold urticaria induced with TempTest 4.0 (positive result). **F**, Cold urticaria induced with TempTest 4.0 (threshold at 24°C; same patient as in **E**). **G**, Cholinergic urticaria (positive result after standardized provocation testing); upper chest. **H**, Cholinergic urticaria (positive result after standardized provocation testing); volar forearm. Provocation threshold testing is documented in standardized protocols (Figure 3). CIndU, Chronic inducible urticaria; UV, ultraviolet.

Recently, it was shown that omalizumab, in doses of 150 and 300 mg, results in a high rate of complete and partial responders in patients with ColdU and a pronounced overall reduction in disease activity.^{22,73} The results of this study show that patients with ColdU unresponsive to antihistamine treatment benefit from a treatment with omalizumab. Antibiotic treatment with doxycycline or penicillin for several weeks induced remission in some patients.^{71,74} Desensitization is a procedure with repeated cold exposure inducing the reduction in skin sensitivity to cold. However, this treatment can induce an anaphylactic shock during induction and should therefore only be performed under expert physician supervision.¹⁴ Maintenance of tolerance requires daily cold showers or baths. A study of 23 patients using cold baths found increased cold temperature tolerance within days of therapy. But when contacted many years later, all patients had stopped therapy within months of the study despite these positive effects.⁷⁵ Thus, cold desensitization therapy is unlikely to be an effective long-term therapy.

Leukotriene receptor antagonists alone or along with antihistamines have been reported to be beneficial in cases of ColdU.^{76,77} Cyclosporine, anakinra (anti-IL-1), etanercept (TNF inhibitor), and ultraviolet B therapy reportedly showed

beneficial responses in selected cases.⁷⁸⁻⁸¹ Reslizumab, an anti-IL-5 antibody, effectively reduced the symptoms of CSU and ColdU in a case study.⁸²

CHOLINERGIC URTICARIA

Clinical features

CholU is characterized by itching, redness, and papular whealing induced by exercise and passive warming (eg, hot bath). Emotional stress as well as spicy and hot food can also provoke these symptoms. Typically, these patients show tiny, short-lived wheals with a pronounced flare reaction that is frequently localized to the trunk and extremities⁸³⁻⁹⁰ (Figure 2, **G** and **H**) and lasts for 15-60 minutes. But other morphological patterns, including angioedema and systemic reactions, can also be observed. CholU must be differentiated from exercise-induced anaphylaxis, which is an anaphylactic reaction induced by physical activity only,⁹¹ which might be food or drug dependent. In exercise-induced anaphylaxis, the skin symptoms usually start with distal pruritus (palmar, plantar, ears) followed by flushing and an erythematous or urticarial rash with larger lesions. In contrast, CholU usually starts with small wheals, which may later

A

Patient information

Name:

Date of birth:

Abbreviations: W = Weal
E = Erythema
A = Angioedema
I = Itch

Document skin reaction with + or -

Provocation tests for inducible urticaria

Symptomatic dermographism (Urticaria factitia)

Testsite: Volar forearm or Upper back
Test: Moderate stroking of the skin with a blunt smooth object (e.g. closed ballpoint pen tip, wooden spatula),
dermographic tester (36 g/mm²), or FricTest (longest pin)
Reading time: 10 minutes after testing

W	I

Date / Time _____ Test done by _____

Positive test = weal & itch: Test trigger strength threshold →

Cold urticaria

Testsite: Volar forearm
Test: Melting ice cube in thin plastic bag, TempTest (4°C) for 5 minutes
Reading times: 10 minutes after testing

W

Date / Time _____ Test done by _____

Positive test = weal: Test temperature threshold →

Heat urticaria

Testsite: Volar forearm
Test: Heat source, TempTest (44°C) for 5 minutes
Reading times: 10 minutes after testing

W

Date / Time _____ Test done by _____

Positive test = weal: Test temperature threshold →

Delayed pressure urticaria

Testsite: Shoulder or Upper Back or Thighs or Volar forearm
Test: Suspension of weights over shoulder (7 kg, shoulder strap width: 3 cm) for 15 min or weighted rods (1.5 cm diameter: 2.5 kg; or 6.5 cm diameter: 5 kg) for 15 min. Dermographic tester at 100 g/mm² for 70 sec
Reading times: ≈6 hours after testing

A	E

Date / Time _____ Test done by _____

Positive test = angioedema & erythema: Test trigger strength threshold →

Solar urticaria

Testsite: Buttocks
Test: UVA 6 J/cm² & UVB 60 mJ/cm² (e.g. Saalman Multitester SBC LT 400) & visible light (projector)
Reading times: 10 minutes after testing

	W
UVA	
UVB	
Visible light	

Date / Time _____ Test done by _____

Positive test = weal: Test trigger strength threshold (UVA / UVB) →

Vibratory urticaria/angioedema

Testsite: Volar forearm
Test: Vortex vibrator for 10 minutes, 1000 rpm
Reading times: 10 minutes after testing

A	W

Date / Time _____ Test done by _____

Positive test = angioedema or weal

Cholinergic Urticaria

Test 1: Exercise machine, e.g. bicycle trainer or treadmill. Exercise for 30 min, increase pulse rate by 3 beats/min every minute, **positive test = weals. If positive, wait > 24 hours and perform**
Test 2: 42 °C bath, monitor body temperature. Continue bath for 15 min after body temperature has increased by ≥ 1°C over baseline
Reading times: During test as well as immediately and 10 minutes after end of test

Test 1.	W	How long after begin of test?
Exercise		_____ minutes

→

Test 2.	W
Hot bath	

FIGURE 3. Protocols for A, provocation and B, threshold testing of chronic inducible urticarias.

B**Patient information**

Name: _____

Date of birth: _____

Abbreviations: W = Weal
E = Erythema
A = Angioedema
I = Itch

Document skin reaction with + or -

Threshold tests for inducible urticaria**Symptomatic dermographism (Urticaria factitia)**

Testsite: Volar forearm / Upper back
Test: Use a dermatographometer (e.g. dermatographic tester or FricTest)
Reading time: 10 minutes after testing
Threshold: Lowest trigger strength that results in weal and itch

FricTest	W	I
Pin 1 (shortest)		
Pin 2		
Pin 3		
Pin 4 (longest)		

Dermatographic tester	W	I
Minimum trigger strength in g/mm ²	_____ g/mm ²	_____ g/mm ²

Test done by _____

Date / Time _____

Cold urticaria

Testsite: Volar forearm
Test: Use TempTest for 5 minutes
Reading time: 10 minutes after end of testing
Threshold: Highest temperature that results in weal

Weal from 4°C to _____ °C

Test done by _____

Date / Time _____

Heat urticaria

Testsite: Volar forearm
Test: Use TempTest for 5 minutes
Reading time: 10 minutes after end of testing
Threshold: Lowest temperature that results in weal

Weal from 44°C to _____ °C

Test done by _____

Date / Time _____

Delayed pressure urticaria

Testsite: Volar forearm (rod), upper back (dermatographic tester)
Test: DPU test device, 15 minutes, diameter of applicator: 6.5 cm,
Reading times: ≈6 hours after testing
Threshold: Rod with lowest weight that results in angioedema and erythema

kg	A	E
1		
2		
3		
4		
5		

Test done by _____

Date / Time _____

Solar urticaria

Testsite: Buttocks
Test: UVA / UVB irradiation (e.g. Saalman Multitester SBC LT 400)
Reading times: 10 minutes after testing
Threshold: Lowest dose of irradiation that results in weal

UVA (J/cm²)	W	UVB (mJ/cm²)	W
2.4		24	
3.3		33	
4.2		42	
5.1		51	
6.0		60	

Test done by _____

Date / Time _____

converge into larger ones. A key differentiating factor is that passive heating (eg, hot baths, showers) does not induce exercise-induced anaphylaxis, while passive heat is a common trigger for ChIU. ChIU is frequently associated with an atopic disposition,⁹² especially in patients with early onset of disease.⁹³

Diagnostic workup

Provocation testing should be performed to confirm ChIU and to rule out exercise-induced anaphylaxis. Caution is advised in patients with pre-existing cardiac problems. Moderate physical exercise appropriate to the patient's age and general condition should be undertaken (eg, on a stationary bicycle) (Figure 1, G). Exercise should be performed according to a standardized protocol.⁹⁴ Wearing warm clothing in a warm room facilitates the provocation tests. The test is positive if exercise challenge leads to the typical rash over 10 minutes. If the exercise provocation test is positive, a passive warming test should be carried out (at least 24 hours later, 42°C full bath for up to 15 minutes, body temperature should increase by $\geq 1.0^{\circ}\text{C}$) to exclude exercise-induced anaphylaxis.

Recently, a standardized protocol for diagnosing and measuring trigger thresholds using pulse-controlled ergometry has been published.⁹⁴ For this pulse-controlled ergometry test, patients are seated on a bicycle ergometer and instructed to cycle in a pulse-controlled manner, that is, to speed up or slow down their pedaling speed to achieve an increase in pulse rate by 3 beats per minute to a final maximum increase of 90 beats per minute above the starting level at 30 minutes. Time to whealing correlates with disease activity; in other words, the sooner the wheals appear, the more active the ChIU. Disease-specific QoL impairment in patients with ChIU is assessed by use of the ChIU-QoL questionnaire.⁹⁵

Treatment

In severely affected patients with ChIU, the avoidance of overheating is essential, but almost impossible. Symptomatic treatment is the first-choice therapy for ChIU. Nonsedating second-generation H1 antihistamines^{96,97} and up dosing in nonresponders are effective in some patients.⁹⁸ There are single reports on the efficacy of omalizumab,^{99,100} scopolamine butylbromide,¹⁰¹ methantheliniumbromide,¹⁰² combinations of propranolol, antihistamines, and montelukast,¹⁰³ as well as treatments and injections with botulinum toxin.¹⁰⁴ Desensitization protocols involving regular physical exercise or treatment with autologous sweat have been described to be of benefit in some patients.^{105,106} High doses of danazol (600 mg daily) were reported to be effective. However, the side-effect profile of danazol restricts its use,¹⁰⁷⁻¹⁰⁹ and dosing should be minimized.

DELAYED PRESSURE URTICARIA

Clinical features

Patients with DPU develop delayed cutaneous erythema and edema with often marked subcutaneous swelling after a pressure stimulus. When this swelling involves the hands or feet, it is indistinguishable from angioedema. Pressure-induced lesions typically occur 4 to 6 hours later, but may occur as early as 30 minutes and last up to 48 hours.¹¹⁰ It is important to note that many patients with DPU also have concomitant CSU and angioedema, and hence many of their lesions may not be exclusively pressure-related. Furthermore, many patients with

CSU, can have lesions that worsen at pressure sites (eg, beneath belts, bra straps). In a study of 135 patients with CSU who underwent systematic challenge tests for pressure-related urticaria, almost 40% had challenge test results consistent with DPU.¹¹¹ Historical features that aid in identifying patients with DPU include delayed urticarial lesions from shoulder straps, riding a bicycle, leaning against furniture, wearing seat belts, tight clothing, and bra straps. Swelling of the feet may result from walking, jogging, or tight shoes. Swelling of the hands may result from carrying shopping bags or using a screwdriver or hammer. The pathogenesis of DPU is unclear; however, both lesional and nonlesional skin have shown increased immunoreactivity of TNF- α and IL-8 in the epidermis.¹¹²

Diagnostic workup

A common method of testing for DPU is referred to as the "sand bag test." This test can be performed by using 15 lbs of weights attached to a strap applied to the shoulder, thigh, or forearm for 15 minutes and observing the site over the next 24 hours for evidence of urticaria or edema.¹¹³ This technique is not standardized and is not as reproducible as other methods. A dermatographometer applied at 100 g/mm² (981 kPa) for 70 seconds on the upper back is a recommended technique with greater reproducibility.⁹⁰ Another diagnostic technique is the use of weighted metal rods stabilized by a frame that may be lowered vertically onto the skin of the thigh, back, or forearm. However, there are several different weights and calibers of rods that have been used by different investigators.^{110,111,114} The test site for pressure provocation testing is considered positive when a red palpable swelling is noted at the test site(s) approximately 6 hours after application (Figure 2, D).

Treatment

Patients with DPU are recommended to avoid tight fitting clothing and favor softer, looser fitting shoes. Activities that exacerbate DPU may need to be modified or stopped. Although antihistamines should be used as in other cases of CIndU, many patients with DPU are resistant to antihistamines. A number of alternative agents have been reported to be efficacious in DPU in small case series or isolated case reports, including corticosteroids, dapson, montelukast, sulfasalazine, escitalopram, oral coumarins, tranexamic acid, theophylline, intravenous immunoglobulin, and TNF inhibitors.¹¹⁵⁻¹²⁵ Omalizumab has been shown to be effective in 3 cases of DPU.¹²⁶

OUTLOOK AND UNMET NEEDS

Over the past few years, novel tools for the diagnostic workup and new treatment options for patients with SD, ColdU, ChIU, and DPU have become available. Less frequent forms of CIndU, however, are still in need of further studies and the development of tools to better manage them in clinical practice.^{20,73,90} Standardized provocation and threshold testing protocols need to be developed for all CIndUs. Their use in diagnosing and monitoring CIndUs helps physicians and patients to understand which triggers are relevant and to optimize disease management. Disease activity scores, disease severity assessment tools, and QoL questionnaires are available for some, but not all CIndUs (Table III). They need to be developed for all. This will help their management in routine clinical practice and will allow us to investigate current and future treatments for their efficacy and safety. As of now, we do not have biomarkers for any CIndU,

neither for disease activity nor for the prognosis, and further studies are needed for their identification and characterization. The efficacy of antihistamines, at standard and higher than standard doses, has not been investigated in most CIndUs. Omalizumab has been shown, in controlled trials, to be effective in ColdU and SD, but its use in all CIndUs is off label. Further studies of these treatment options are needed, as is the development of new ones. Finally, more research on the etiopathogenesis of CIndUs is needed to identify and characterize their underlying causes and find a cure.

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