

Management of Inducible Urticarias

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Abstract

Purpose of review This review aims to update the information and latest advances in chronic inducible urticarias.

Recent findings In contrast to chronic spontaneous/idiopathic urticarias, chronic inducible urticarias are associated with a specific trigger and factor. One must accurately identify and characterize the specific trigger for distinguishing chronic spontaneous/idiopathic urticaria and chronic inducible urticarias. The latter are diagnosed based on patient history and results of provocation testing which contribute to confirm the exact diagnosis, assess the threshold, and determine the severity of the disease. The general management of chronic inducible urticarias includes the identification and avoidance of the specific trigger, and symptomatic treatment with the goal of reaching complete symptom control. Symptomatic treatment for chronic inducible urticarias targets the blocking of mast-cell mediators (H₁-antihistamines, H₂-antihistamines, leukotriene antagonists) and inhibition of mast-cell activation (omalizumab, cyclosporine, phototherapy). H₁-antihistamines are fundamental treatments for chronic inducible urticarias, but H₁-antihistamine-

resistant cases are not rare and additional treatment is often necessary. Also, therapeutic reactivity varies according to each subtype and patient.

Summary Notably, some subtypes of chronic inducible urticaria can be treated by desensitization and/or tolerance induction to triggers. In contrast, the underlying pathogenesis of chronic inducible urticaria is not known and further studies are needed to better clarify its etiology.

Introduction

“Inducible urticarias” are a distinct subgroup of urticarias in which a specific external trigger induces reproducible itchy wheals and/or angioedema. The European Academy of Allergy and Clinical Immunology (EAACI)/Global Allergy and Asthma European Network (GA²-LEN)/European Dermatology Forum (EDF)/Urticaria Network e.V. (UNEV) consensus defined “chronic inducible urticaria” to be a subgroup of chronic urticaria characterized by the recurrence of itchy wheals and/or angioedema for ≥ 6 weeks [1]. Within the group of chronic inducible urticarias, symptomatic dermographism/urticaria factitia, cold urticaria, heat urticaria, delayed pressure urticaria, solar urticaria, and vibratory angioedema are defined as “physical urticarias.” Non-physical chronic inducible urticarias include cholinergic urticaria, contact urticaria, adrenergic urticaria, and aquagenic urticaria (Table 1) [2••]. Patients with immediate-type food and/or drug allergy can reproduce urticarial symptoms by causative foods and/or drugs, but these symptoms are not included in chronic inducible urticaria as a definition.

Chronic inducible urticarias are diagnosed on patient history and the results of provocation testing. The underlying pathogenesis in chronic inducible urticaria is not well clarified. Therefore, the diagnostic workup in

chronic inducible urticaria aims at confirming the diagnosis of the subtype as well as assessment of disease activity and trigger thresholds.

Treatment should focus on the avoidance of the trigger and symptomatic treatment. Chronic inducible urticarias are chronic, last several years, and are often resistant to first-line therapy with H₁-antihistamines [2••]. In addition, uncontrolled chronic urticaria refractory to H₁-antihistamines has a high prevalence of co-occurrence with chronic spontaneous urticaria and chronic inducible urticaria [3, 4]. Therefore, chronic inducible urticarias are debilitating and impact quality of life (QoL) severely. Some chronic inducible urticarias can be treated by desensitization to triggers. Recently, a strong body of evidence has supported the use of omalizumab in the treatment of patients with conventional therapy-refractory chronic inducible urticaria [5•]. Nonetheless, management of refractory chronic inducible urticarias remains difficult, and further need of therapeutic options corresponding to each subtype is high.

Here, we review the current important and interesting new findings on the pathophysiological mechanism, classification, diagnostic methods, and management of chronic inducible urticarias.

Classification, diagnostic methods, and pathogenesis of chronic inducible urticaria

Chronic inducible urticarias are diagnosed and classified on patient history and the results of provocation testing. Physical urticarias and non-physical urticarias are included in the definition of chronic inducible urticaria.

Physical urticarias are defined in current international guidelines as a group of diseases in which wheals and/or angioedema are induced reproducibly by external physical stimuli [6••]. Symptomatic dermographism/urticaria factitia, cold urticaria, heat urticaria, delayed pressure urticaria, solar urticaria, and vibratory angioedema are physical urticarias. Cholinergic urticaria, contact

Table 1. Classification of chronic inducible urticaria

Chronic urticaria subtypes	
Chronic spontaneous urticaria	
	Chronic inducible urticaria
	Physical urticaria
	Symptomatic dermographism
	Cold urticaria
	Delayed pressure urticaria
	Solar urticaria
	Heat urticaria
	Vibratory angioedema
	Other inducible urticaria
	Cholinergic urticaria
	Contact urticaria
	Aquagenic urticaria
	Adrenergic urticaria

urticaria, adrenergic urticaria, and aquagenic urticaria are not included in physical urticarias because their wheal formation is not induced by a physical stimulus [7, 8].

Chronic inducible urticarias have been estimated to be present in $\leq 5\%$ of the general population, and in 10–50% of patients with chronic urticaria [9]. The most common form of chronic inducible urticaria is symptomatic dermographism (1–5% in the general population), and cholinergic urticaria (4–11.2% of population) [2••, 10, 11]. The next most common form of chronic inducible urticaria is cold urticaria, and the prevalence of all physical urticarias is 5–30% [12]. The duration of chronic inducible urticaria has been estimated to be several years [2••].

Physical urticaria

Symptomatic dermographism/urticaria factitia

Symptomatic dermographism is the most common type of physical urticaria. It is characterized by wheals and accompanied by itching and/or burning sensations after moderate stroking of the skin. Symptomatic dermographism should be differentiated from simple dermographism in which whealing (but not itching) occurs after firm stroking of the skin because the whealing response is conspicuous in 5% of healthy young people [13]. One questionnaire survey of patient opinion revealed that the mean duration of symptomatic dermographism was 6.25 years, and that symptomatic dermographism is a debilitating condition with profound effects on QoL [14].

The underlying pathogenesis in symptomatic dermographism is not well clarified. Degranulation of mast cells and the associated increase in plasma levels of histamine occurs in dermographic skin, and mast cells are needed to

induce dermographism [15]. The latter can be transferred passively with immunoglobulin (Ig)E and, occasionally, IgM [16]. It has been postulated that an antigen induced by mechanical stimulation of the skin induces specific antibodies directed against IgE.

The diagnosis of symptomatic dermographism is confirmed by stroking the skin with a smooth, blunt object such as a wooden spatula or tip of a ballpoint pen. This test is considered to be positive if a pruritic wheal is present within 10 min of provocation. A wheal response without itching suggests simple dermographism.

A calibrated dermographometer is an instrument that applies pressure varying between 20 g/mm² (196 kPa) and 160 g/mm² (1569 kPa). The development of a pruritic palpable wheal to applied pressure of <36 g/mm² is considered diagnostic of symptomatic dermographism [7]. Recently, a simpler tester used to investigate patients with symptomatic dermographism was developed: Fric Test® (Moxie, Berlin, Germany) [17] (Fig. 1a). This instrument consists of a distinguishable plastic comb with four tips of length 3.0, 3.5, 4.9, and 4.5 mm. It applies graded shearing forces to the skin to allow determination of the trigger

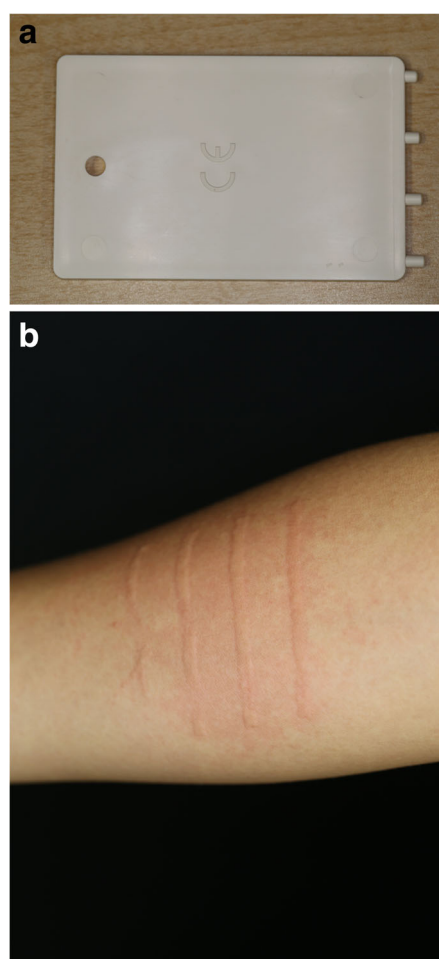


Fig. 1. **a** Fric Test® instrument. **b** Positive result of the Fric Test.

threshold. A response to dermographic testing is considered positive if a pruritic palpable wheal of width ≥ 3 mm is present within 10 min of provocation (Fig. 1b).

Cold urticaria (also known as acquired cold urticaria or cold contact urticaria)

Cold urticaria encompasses various syndromes in which a cold stimulus induces urticaria. Cold urticaria is the second most common form of physical urticaria and estimated to be present in 2% of urticaria patients [18].

Typically, symptoms appear rapidly and include pruritic erythema and wheals upon exposure to cold air, liquids, or solids that last ≤ 1 h [19]. Extensive contact with cold air may provoke systemic symptoms such as dyspnea, hypotension, and loss of consciousness in addition to generalized wheals that resemble anaphylaxis [20].

“Acquired cold urticaria” is subdivided into primary and secondary types, which are different designations in accordance with an unknown (primary) or suspected (secondary) underlying cause or disease, respectively. There are rare subforms of acquired cold urticaria that cannot be diagnosed by cold-contact stimulation tests (e.g., ice-cube test) because symptoms occur from exposure to unique environmental conditions [12]. It has been suggested that these entities should be classified as “atypical acquired cold urticaria.” Among the types of atypical acquired cold urticaria, a very rare form is inherited as an autosomal-dominant trait. Cryopyrin-associated periodic syndromes (CAPSs) are a group of rare auto-inflammatory disorders. Many cases of CAPS are caused by mutation in *NLRP3* and increased secretion of interleukin (IL)-1. CAPS include three variants, including a familial cold auto-inflammatory syndrome as a mild form of CAPS, which was previously termed “familial cold urticaria” [21]. In familial cold auto-inflammatory syndrome, cold-contact stimulation tests usually elicit a negative response [22]. Several subtypes of atypical acquired cold urticaria have been proposed (Table 2) [12, 23, 24].

The diagnosis of acquired cold urticaria is confirmed by cold-provocation methods such as the ice-cube test, testing with cool packs or cold water baths, and *TempTest*® (CK Electronics, Köln, Germany). A positive result for a cold-contact stimulation test consists of a wheal-and-flare reaction observed during rewarming of the skin to ambient temperature (Fig. 2). *TempTest*® is useful to establish the critical temperature thresholds (highest temperature) that induce a wheal-and-flare reaction [25]. Simultaneous application of 12 temperatures from 4.0 to 42 °C allows evaluation of the critical temperature threshold and cold stimulation time threshold, which helps to define disease severity [2••].

Heat urticaria

Heat urticaria is one of the rarest forms of physical urticaria, with only 60 published cases. It is defined by well-demarcated wheals limited to skin that has been exposed to heating within minutes of exposure. Most cases occur in female patients aged 20–45 years [26]. The main differential diagnoses are cholinergic urticaria, exercise-induced anaphylaxis, and solar urticaria because the prevalent triggers (e.g., sun exposure and bathing) may be relevant [27]. Accordingly, the diagnosis of heat urticaria should be secured by appropriate provocation testing. The diagnosis is confirmed by application of a hot stimulus to the skin of the volar forearm (e.g., a metal/glass cylinder filled with hot water

Table 2. Examples of differential diagnoses of classic acquired cold urticaria

Atypical cold urticaria	Diagnostic distinction
Atypical acquired cold urticaria	Immediate CST-negative
Delayed cold urticaria	Delayed development of urticarial lesions up to 24 h after testing
Cold-dependent dermographism	Induction of dermographism only in areas that had been exposed to cold
Cold-induced cholinergic urticaria	Induction of urticarial symptoms by exercise in cold environments
Localized reflex cold urticaria	Induction of small wheals in the vicinity of, but not in the area of, contact with an ice cube
Hereditary subtypes of cold urticaria	
Familial cold autoinflammatory syndrome (CAPS)	Episodic cold-induced urticarial-like lesions associated with conjunctival injection, fever, and other systemic inflammatory symptoms; often delayed development of lesions (1–2 h)

or hot-water baths up to 44 °C for 5 min with a 10-min observation period). *TempTest*® can be useful to establish the critical temperature threshold (lowest temperature) that will induce a wheal-and-flare reaction. Although the underlying pathogenesis of heat urticaria is not well clarified, some reports have stated that serum factors activated by heat stimulation are responsible for the development of the whealing reaction [28–30].

Delayed pressure urticaria

Delayed pressure urticaria is characterized by the development of swelling that occurs at sites of sustained pressure on the skin after a delay of ≥ 30 min [31–33]. Responses occur between 30 min and 12 h (usually 6–8 h) of skin exposure to a sustained pressure stimulus and may last ≤ 72 h. Delayed pressure urticaria as the predominant or only problem is uncommon; 37–62% of patients have coexistent chronic spontaneous urticaria [33, 34]. The lesions of delayed pressure urticaria tend to appear at trouser waistlines/buttocks after



Fig. 2. A positive result for a contact stimulation test (20 °C) for 5 min.

prolonged sitting down, and on feet soles after prolonged walking/standing. Delayed pressure urticaria may be associated with influenza-like symptoms such as fever, chills, and/or arthralgia [31]. The underlying mechanism of delayed pressure urticaria is not known. Histological examination of delayed pressure urticaria has revealed a reduced number of stainable mast cells, predominant infiltration of neutrophils in early lesions, and eosinophil infiltration in late lesions [34, 35]. Increased levels of IL-6, C-reactive protein, and adhesion molecules (e.g., E-selectin and vascular cell adhesion protein-1), high plasma concentrations of platelet-specific chemokines (e.g., platelet factor 4, beta-thromboglobulin, and soluble CD40L) have been reported [36–38].

The diagnosis of delayed pressure urticaria can be confirmed by challenge with a weight of 7 kg on a 3-cm shoulder strap suspended over the patient's shoulder for 15 min, or weighted rods (a diameter of 1.5 cm using 2.5 kg; a diameter of 5.5 cm using 5 kg) for 15 min. When testing with a dermatographometer, the device should be applied perpendicularly at 100 g/mm² for 70 s [2••]. A positive result is the development of urticaria and/or angioedema at the pressure site after 4–6 h. The reaction is not accompanied by pruritus, but may be accompanied by burning/painful sensations.

Solar urticaria

Solar urticaria is a relatively rare photodermatosis. It is defined by the development of well-demarcated wheals within minutes after skin exposure to sunlight at ultraviolet (UV)B (280–320 nm), UVA (320–400 nm), or visible (400–700 nm) wavelengths (Fig. 3a). Patients develop wheals by exposure to specific wavelengths of light called “action spectra,” which variably include the broad or narrow spectra distributed among visible light: UVA and UVB. Some patients with an “inhibition spectrum” (which suppresses the whealing response when it is irradiated before, during, and immediately after irradiation of the action spectrum) in solar urticaria develop a delayed urticarial reaction after sunlight exposure [39, 40]. Solar urticaria is usually idiopathic and rarely secondary to porphyrias, drugs, or chemicals [41, 42].

The diagnosis of solar urticaria is based on history and the results of provocation phototests. Provocation testing with solar simulators (UVA and UVB) and slide projectors (visible light) should be carried out on the buttocks, abdomen, and back because covered body areas are more sensitive than sun-exposed areas such as the face or hands. In patients with solar urticaria, provocation usually leads to an urticarial response at exposure sites within 10 min (Fig. 3b).

The underlying pathogenesis of solar urticaria is not well clarified, but etiologies other than physical urticarias have been proposed. Patients with solar urticaria have specific action spectra. Wavelength-specific cutoff filters and monochromators help to determine more precise action spectra. Autologous sera which have been irradiated previously *in vitro* at the action spectrum induce wheal-flare responses in most patients with solar urticaria [43] (Fig. 3c). This response indicates that the wheal-forming factor is produced by light energy in the patient's serum [43, 44]. The molecular weight of this photoallergen is different from 25 to 45 kD, 300–1000 kD in each case, but the responsible photoallergen in solar urticaria has not been identified. Studies on passive transfer and the effectiveness shown by omalizumab against solar

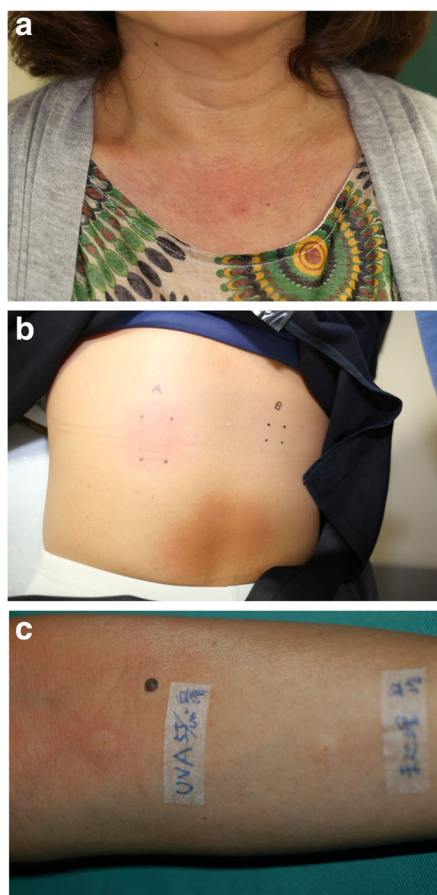


Fig. 3. **a** A clinical picture of solar urticaria. Wheal and erythema can be observed on the sun-exposed area. **b** A positive result of provocation testing using solar simulators (UVA and UVB) and a slide projector (visible light). UVA and visible light (but not UVB) phototesting are positive. **c** Intradermal testing with autologous UVA-irradiated serum is positive, but the test with non-irradiated serum is negative.

urticaria suggest that the transferable serum factor is IgE, and that IgE is associated with the pathogenesis of solar urticaria [45, 46].

Vibratory angioedema

Patients with vibratory angioedema experience pruritus and swelling minutes after skin exposure to a vibratory stimulus (e.g., drills used in dentistry or by building workers). The diagnosis of vibratory angioedema can be confirmed by application of a vortex mixer to the skin of the volar forearm. The vortex mixer is vibrated at a constant speed of 780–1380 rpm for ≥ 1 min and ≤ 5 min [47]. The application site should be assessed for swelling 10 min after testing [2••].

Non-physical inducible urticaria

Cholinergic urticaria

Cholinergic urticaria was described first by Duke in 1924 [13]. It is a frequently occurring skin disorder characterized by unique clinical features. Pinpoint,

highly pruritic wheals with surrounding erythema, usually 1–3 mm in diameter, occur after sweating induced by an increase in the core body temperature, which occurs in response to a hot bath, physical exercise, and/or emotional stress [48] (Fig. 4). Occasionally, these wheals may become larger and coalesce with one another (Fig. 4). In contrast to other types of urticaria, many patients with cholinergic urticaria complain that they feel “stinging” or “tingling” pains, and these feelings appear to hamper their QoL [49]. Based on whether the clinical episode has developed secondary to exercise and/or heat stimulation, cholinergic urticaria must be differentiated from food-dependent, exercise-induced anaphylaxis and heat urticaria. Similar clinical images develop after many types of stimulation excluding exercise and/or heat stimulation, so cholinergic urticaria should be differentiated from aquagenic urticaria, adrenergic urticaria, and cold-induced cholinergic urticaria [24, 50, 51]. The physiopathologic mechanism of cholinergic urticaria has not been well clarified, but it is thought that histamine, cholinergic agents (e.g., acetylcholine), sweat allergy, serum factors, poral occlusion, and anhidrosis are related to development of the symptoms of cholinergic urticaria [52–55].

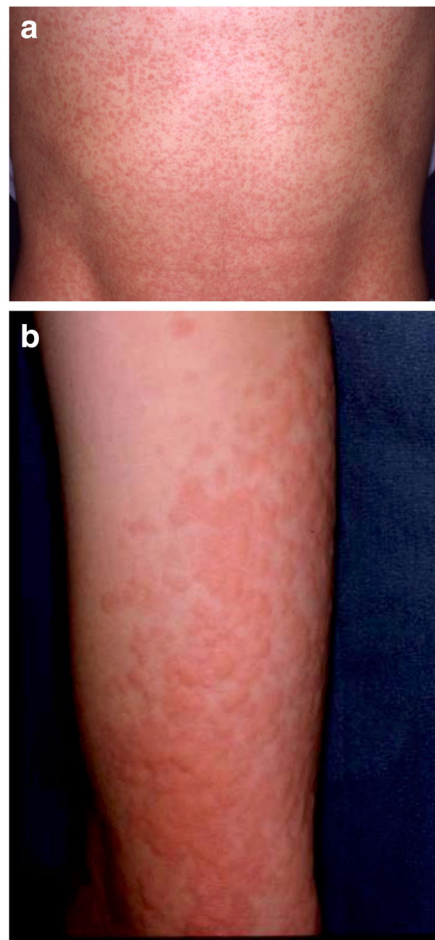


Fig. 4. **a** Typical appearance of cholinergic urticaria: pinpoint-sized, highly pruritic wheals with surrounding erythema occur on the trunk after sweating. **b** Occasionally, the wheals become larger and coalesce with one another.

Four pathogenesis- and/or clinical feature-based subtypes of cholinergic urticaria were proposed recently: (i) conventional sweat allergy-type cholinergic urticaria without angioedema, (ii) follicular-type cholinergic urticaria with a positive result for the autologous serum skin test, (iii) cholinergic urticaria-palpebral angioedema, and (iv) cholinergic urticaria with acquired anhidrosis and/or hypohidrosis [50, 52, 56, 57]. Subtypes (i), (ii), and (iii) must be differentiated from subtype (iv), especially in terms of sweating, because the therapeutic approach is quite different [50, 58].

Provocation tests for the diagnosis of cholinergic urticaria are done by increasing the body temperature through exercise (treadmill or stationary bicycle) or use of a hot bath (42 °C for 15 min) [1, 59, 60]. The EAACI/GA²LEN/EDF/UNEV Consensus Panel states that an increase in core body temperature by >1.0 °C over the baseline as indicated by a passive warming test involving sitting for ≤15 min in a bath full of water at 42 °C confirms the diagnosis of cholinergic urticaria. Recently, a standardized protocol for diagnosing and measuring the thresholds of cholinergic urticaria using pulse-controlled ergometry was proposed [61].

Contact urticaria

Contact urticaria is defined by the development of urticarial lesions usually within 30 min after contact to an exogenous agent. Wheals are provoked by IgE-mediated or non-immunologic mechanisms. Common eliciting factors include foods, plant components, latex, drugs, cosmetics, industrial chemicals, animal products, or textiles [62]. After thorough history-taking, provocation testing should be carried out to confirm IgE-mediated or non-immunologic contact urticaria using open application tests, skin-prick tests, or closed patch tests for 20 min.

Adrenergic urticaria

Adrenergic urticaria is rare type of stress-induced physical urticaria [63]. Adrenergic urticaria is characterized by widespread pruritic, urticarial papules triggered by stress, trauma, or emotional upset, but not by heat or exercise [63, 64]. The diagnosis can be made by intradermal injection of adrenaline or noradrenaline, which produces a characteristic rash. The clinical picture of adrenergic urticaria resembles that of cholinergic urticaria but a positive noradrenaline test and negative acetylcholine skin test are distinctive features in adrenergic urticaria but not cholinergic urticaria, and a white “halo” of vasoconstriction surrounding small red or pink wheals is also characteristic of adrenergic urticaria.

Aquagenic urticaria

Aquagenic urticaria was described first by Shelley and Rawnsley in 1964. It is a rare form of contact urticaria triggered by various forms of water—regardless of its temperature [65]. Aquagenic urticaria is a rare variant of chronic inducible urticaria and shares features of physical urticaria and contact urticaria [66]. The condition is characterized by follicular wheals, generally 1–2 mm in size, with an erythematous flare within 20–30 min on sites exposed to water which disappear within 30–60 min. The condition must be differentiated from aquagenic pruritus, cholinergic urticaria, cold urticaria, and heat urticaria [67].

These differential diagnoses should be ruled out before testing for aquagenic urticaria.

The mechanism of action of aquagenic urticaria is poorly understood. It has been proposed that water carries an epidermal antigen to sensitized mast cells [68]. For the diagnosis of aquagenic urticaria, a compress or towel soaked with water at 35–37 °C or physiologic saline is placed on the patient's trunk. The compress or towel can be removed after ≤40 min if the patient reports pruritus and the first wheals are seen at the skin test site. The test is positive if urticarial lesions develop inside the contact area within 10 min after taking off the compress/towel [2••]. If such a test using a damp compress is negative, immersing the affected body parts in water or asking patients to take a bath or shower may be attempted [67].

Treatment

Diagnostic measures do not reveal the underlying causes or lead to specific therapeutic options, so the diagnostic workup for chronic inducible urticaria should be limited to confirmation of the diagnosis and assessment of disease activity by monitoring trigger thresholds. Treatment should focus on avoidance of the physical trigger and symptomatic treatment with the goal of reaching complete control of the signs and symptoms of chronic inducible urticaria [2••].

Symptomatic treatment for chronic inducible urticaria includes non-sedating H₁-antihistamines in conventional doses. A dose increase of up to fourfold can be instigated if the response is not satisfactory, and alternative and/or additional medications (leukotriene antagonists, H₂-antihistamines, omalizumab, cyclosporin A) tried [49, 69–72]. However, this statement is a general recommendation because therapeutic reactivity varies according to each subtype and patient. For some forms of chronic inducible urticaria, tolerance induction can be achieved by progressive and controlled long-term exposure to the stimulus. This approach has been applied to cold urticaria [73, 74], heat urticaria [26, 28, 75], solar urticaria [44, 76], and cholinergic urticaria [77].

Pharmacologic treatment (optional heading)

Class of drug: H₁-antihistamines (second-generation) [2++]

Standard dosage	Oral: licensed dose
Contraindications	Hypersensitivity to each drug
Main drug interactions	Alcohol ↑, erythromycin ↑
Main side effects	Sleepiness, fatigue
Special points	Dose up to fourfold (in patients who do not respond to the licensed dose)
Cost/cost-effectiveness	Inexpensive

Class of drugs: leukotriene antagonists [2+ in some subtypes]

Standard dosage	Oral: 10 mg daily (montelukast)
Contraindications	Hypersensitivity to each drug

Main drug interactions	Phenobarbital ↓, CYP3A4-metabolism agents ↑, CYP3A4 inhibitors ↑
Main side effects	Diarrhea, nausea
Special points	Use as add-on therapy to second-generation H ₁ -antihistamines
Cost/cost-effectiveness	Moderate

Class of drug: H₂-antihistamines [2+ in some subtypes]

Standard dosage	Oral: 600 mg every 12 h (cimetidine), 150 mg twice a day (ranitidine), 10 mg twice a day (lafutidine)
Contraindications	None
Main drug interactions	H ₁ -antihistamines ↑ (Due to the inhibition of CYP3A4)
Main side effects	No significant difference in the level of sedation from baseline with H ₁ -antihistamines (use as add-on therapy); hematopathy
Special points	Use as add-on therapy to second-generation H ₁ -antihistamines
Cost/cost-effectiveness	Inexpensive

Class of drug: omalizumab [1+ in some subtypes]

Standard dosage	Subcutaneous injection: 300 mg (150 mg) every 4 weeks
Contraindications	Hypersensitivity to omalizumab
Main drug interactions	None
Main side effects	Hypersensitivity, injection site reaction
Special points	Recommended for patients with chronic inducible urticaria who cannot achieve adequate control of symptoms with conventional therapies
Cost/cost-effectiveness	Expensive

Class of drug: cyclosporin A [3 in some subtypes]

Standard dosage	Oral: 1–5 mg/kg/day
Contraindications	Pregnancy, breastfeeding, tacrolimus, pitacastatin, rosuvastatin, bosentan, aliskiren, asunaprevir
Main drug interactions	CYP3A4 or P-glycoprotein transporter inhibitor or inducer ↑↓
Main side effects	Renal dysfunction, epigastric distress
Special points	Use as add-on therapy to second-generation H ₁ -antihistamines
Cost/cost-effectiveness	Expensive

Class of drug: corticosteroids [3 in some subtypes]

Standard dosage	Oral: 5–30 mg/day (prednisone), 2 mg/day (betamethasone)
Contraindications	Hypersensitivity to corticosteroid
Main drug interactions	Various types of drugs

Main side effects	Mood alternation, hypertension, hyperglycemia, hyperlipoproteinemia, osteopenia, cataracts, gastrointestinal complaints
Special points	No controlled study has been done. Only short-term use to help manage exacerbations should be considered
Cost/cost-effectiveness	Inexpensive

Levels of scientific evidence described above follow the Scottish Intercollegiate Guideline Network (SIGN; BMJ 2001; 323: 334-6)

Interventional procedures (optional heading)

Desensitization and tolerance induction

Standard procedure	Variable procedure according to each subtype
Contraindications	Not determined
Complications	Symptoms due to anaphylactic shock and/or induced urticaria
Special points	Even if tolerance is induced once, patients usually have to be exposed to the triggering factor continuously for a long time to maintain the tolerant condition
Cost/cost-effectiveness	Usually moderate and/or inexpensive, sometimes unnecessary to use a special tool (e.g., heat urticaria, cold urticaria, and solar urticaria)

Phototherapy

Standard procedure	Variable procedure according to each subtype; psoralen and ultraviolet A, narrow-band ultraviolet (UV)B or UVA
Contraindications	Patients with skin malignant tumors, history of malignant tumors of the skin, high risk of carcinogenesis, strong photosensitivity
Complications	Sunburn, bullous formation, pigmentation, photocarcinogenesis (long-term)
Special points	Immunosuppressive effect, reduced degranulation of mast cells, hardening effect (solar urticaria)
Cost/cost-effectiveness	Moderate

Emerging therapies (optional heading)

Omalizumab

Standard dosage	Subcutaneous injection: 300 mg (150 mg) every 4 weeks
Contraindications	Hypersensitivity to omalizumab
Main drug interactions	None
Main side effects	Hypersensitivity, injection-site reaction
Special points	Recommended for patients with chronic inducible urticarias who cannot achieve adequate control of symptoms with conventional therapies
Cost/cost-effectiveness	Expensive

Conclusions

This review focused on the pathophysiologic mechanism, classification, diagnostic methods, and management of chronic inducible urticarias. There has been relatively little progress on the pathophysiologic mechanism of chronic inducible urticarias, but the diagnostic methods and management of chronic inducible urticarias have improved and progressed recently. However, there is less evidence for the management of chronic inducible urticarias than for chronic spontaneous urticaria. Chronic inducible urticarias are often resistant to first-line therapy with H₁-antihistamines, and patients have a reduced QoL. Omalizumab may satisfy an unmet need for conventional treatment-resistant chronic inducible urticarias. The exact differential diagnosis and subtype classification of chronic inducible urticarias is important for selecting the optimal therapeutic method. Further research into the pathogenesis of chronic inducible urticarias should be undertaken.

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Compliance with Ethical Standards

Conflict of Interest

Atsushi Fukunaga declares that he has no conflict of interest. Ken Washio declares that he has no conflict of interest. Mayumi Hatakeyama declares that she has no conflict of interest. Yoshiko Oda declares that she has no conflict of interest. Kanako Ogura declares that she has no conflict of interest. Tatsuya Horikawa declares that he has no conflict of interest. Chikako Nishigori declares that she has no conflict of interest.

Human and animal rights and informed consent

This article does not contain any studies with human or animal subjects undertaken by any of the authors.

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Papers of particular interest, published recently, have been highlighted as:

- Of importance
- Of major importance

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