

Diagnostic Tests for Urticaria

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KEYWORDS

- Diagnosis • Differential diagnosis • Subtypes • Severity • Underground disease
- Complementation • Threshold

KEY POINTS

- Asking adequate clinical questions is essential and an important step in the diagnosis of urticaria and subtypes of urticaria.
- The aims of clinical examinations are to confirm the diagnosis of urticaria subtypes, evaluate disease severity/threshold, and/or find or rule out underlying causes or diseases.
- Provocation tests may be performed for the diagnosis and threshold evaluation of inducible types of urticaria.
- Severity and disease activities of urticaria may be evaluated by questionnaire-based scores, such as UAS-7 (urticaria activity score over 7 consecutive days), AAS (Angioedema Activity Score), CU-Q2oL (Chronic Urticaria Quality of Life Questionnaire), and AE-QoL (Angioedema Quality of Life Questionnaire).
- Certain biomarkers for inflammation, such as serum C-reactive protein and interleukin-6, and blood coagulation/fibrinolysis, such as fibrin degradation products, D-dimer, and prothrombin fragment F1 + 2, may reflect disease severity and activity of chronic spontaneous urticaria.

INTRODUCTION

The manifestation of individual skin symptoms of urticaria is a simple wheal and flare, which, although itchy, disappear without residual signs. On the other hand, the pathogenesis of urticaria is highly heterogeneous. Therefore, there is no single clinical examination commonly required for all patients with urticaria. Moreover, the aims of clinical examinations for urticaria may be variable on a case by case basis. They include confirmation of urticaria subtype, differential diagnoses, threshold determinations, the evaluation of disease activities, and/or to find underlying causes. Thus, the proper performance of diagnostic tests for urticaria is important not only for efficient

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clinical practice for individual patients but also to reduce the socioeconomic problems of urticaria.

CLASSIFICATION OF URTICARIA

Proper diagnosis of the urticaria subtype is important for adequate management of urticaria. At present, the classification proposed by the EAACI (European Academy of Allergology and Clinical Immunology), GA²LEN (Global Allergy and Asthma European Network), EDF (European Dermatology Forum), and WAO (World Allergy Organization) (Table 1) is probably the most widely accepted classification in the world for the management of urticaria.^{1–4} This classification was further clarified by the definition of chronic urticaria⁵ and supplemented by a classification of angioedema in other publications (Table 2).⁶

DIAGNOSIS OF URTICARIA SUBTYPES

A diagnosis of urticaria can be made based on the confirmed appearance of a transient and local skin edema with flare that disappears within a few hours or a day at the most. The skin surface should be smooth and intact, but the size, shape, and color of the eruptions are largely variable and not considered important for determining whether the condition does or does not represent urticaria. This stage of the diagnosis should be completed by careful history taking and clinical examination, especially by inspection.

For the diagnosis of urticaria subtypes, however, various provocation tests and blood examinations may be necessary. All medications for urticaria, especially antihistamines, should be withdrawn; antihistamines should be withdrawn for at least 48 hours before the provocation test, if possible, because they may lead to false-negative results. For this stage of the diagnosis, careful and thorough history taking is again important and information regarding the urticaria eruptions may help in the diagnosis of urticaria subtypes (Table 3). It is important to keep in mind that the same patient may concurrently have multiple urticaria subtypes. In addition, provocation tests should be performed with potential emergency treatment in mind, because

Table 1 Classification of urticaria subtypes proposed by the EAACI/GA ² LEN/EDF/WAO guidelines in 2009	
Types	Subtypes
Spontaneous urticaria	Acute spontaneous urticaria Chronic spontaneous urticaria
Physical urticaria	Cold contact urticaria Delayed pressure urticaria Heat contact urticaria Solar urticaria Urticaria factitia/dermographic urticaria Vibratory urticaria/angioedema
Other urticaria types	Aquagenic urticaria Cholinergic urticaria Contact urticaria Exercise-induced anaphylaxis/urticaria

From Zuberbier T, Asero R, Bindslev-Jensen C, et al. EAACI/GA²LEN/EDF/WAO guideline: definition, classification and diagnosis of urticaria. Allergy 2009;64:1419; with permission.

Table 2
Classification of angioedema

Category	Disease	Notes
Bradykinin-mediated		Not responsive to antihistamines
C1-INH deficient/defect		
Positive inheritance	HAE-1, HAE-2	
Negative inheritance	ACID	Possibly caused by lymphoproliferative disorders, or autoantibody against C1-INH
	Sporadic HAE-1	Both protein and function are low
	Sporadic HAE-2	Only activity is low
Normal C1-INH		
Positive inheritance	HAE with normal C1-INH (type 3)	
Negative inheritance	Drug-induced AE (eg, ACEI)	
Mast cell-mediated		Normal C1-INH
IgE-mediated	Anaphylaxis, IgE-mediated urticaria	
Non-IgE-mediated	Chronic spontaneous urticaria, inducible urticarias, unclassified angioedema	
Idiopathic	Nonclassified angioedema	Normal C1-INH, negative inheritance

Abbreviations: ACEI, angiotensin-converting enzyme inhibitor; ACID, acquired angioedema as a result of C1 inhibitor deficiency; C1-INH, C1-esterase inhibitor; HAE, hereditary angioedema; HAE-1, HAE type 1; HAE-2, HAE type 2.

Modified from Lang DM, Aberer W, Bernstein JA, et al. International consensus on hereditary and acquired angioedema. *Ann Allergy Asthma Immunol* 2012;109:396; with permission.

the patient may develop systemic symptoms including shock. Specific examinations for the diagnosis of urticaria subtypes are summarized in [Table 4](#).

Physical Urticarias

The diagnosis of physical urticarias is made mainly by careful history taking and confirmed by positive physical provocation testing.^{18,19} Because patients with a predominantly nonphysical urticaria may also have 1 or more physical urticarias, all physical triggers that seem to be relevant from the medical history should be tested. Provocation by physical triggers should be performed using adequate strengths of the triggers at appropriate skin sites that have not been recently affected by urticaria. These sites may be refractory for hours or a day after urticarial reactions.¹⁸ Recommended methods for provocation testing for each of the physical urticarias and cholinergic urticaria were described in 2009 by EAACI, GA²LEN, and the urticaria network e.V. (UNEV).¹⁸

Urticaria factitia/dermatographic urticaria/mechanical urticaria

Dermatographic urticaria is a common subtype of physical urticaria, and its symptoms appear in response to lightly stroking the skin. Several instruments for testing this have been developed and used to determine the threshold of individual patients.^{19–21} The forearm is more suitable for this test than the abdomen, back, and shin areas.²⁰

Table 3 Questions for making urticaria and its subtype diagnosis	
<i>Common characteristics of urticaria (to make a diagnosis of urticaria)</i>	
1. Flare (reddish eruption) 2. Wheal (hive; local swelling or superficial skin swelling) 3. Duration of individual eruptions (commonly less than 24 hours except for delayed pressure urticaria and angioedema)	
<i>Specific characteristics of urticaria subtypes (to determine the subtype of urticaria)</i>	
Categories to be Clarified	Corresponding Subtypes of Urticaria
Size	
<~ 5 mm	Cholinergic urticaria, adrenergic urticaria, aquagenic urticaria
>~ 5 mm	Any other subtypes
Shape	
Linear	Mechanical urticaria
Geographic	Mostly spontaneous urticaria, urticarial vasculitis
Area	
Limited to or mostly in exposed body surfaces	Cold contact urticaria, solar urticaria, heat contact urticaria, contact urticaria
Limited to the face	Angioedema, oral allergy syndrome
Duration	
>12 h	Spontaneous urticaria (acute or chronic), delayed pressure urticaria, angioedema, mostly not cholinergic urticaria and the other physical urticarias
Directly related eliciting stimuli	
None	Spontaneous urticaria (acute or chronic)
Friction, shear	Mechanical urticaria
Cold	Cold urticaria
Sun exposure	Solar urticaria, possibly cholinergic urticaria due to sweating
Heat	Heat urticaria, possibly cholinergic urticaria due to sweating
Pressure	Delayed pressure urticaria
Perspiration (sweating), increase of body core temperature	Cholinergic urticaria
Particular substance (intake; foods, drugs)	Allergic urticaria, intolerance, urticaria due to radiographic contrast media, and so forth
Particular substance (contact; plant, chemicals, foods, and so forth)	Contact urticaria
Exercise	Exercise-induced anaphylaxis, cholinergic urticaria due to sweating
Psychological tension	Adrenergic urticaria, cholinergic urticaria due to sweating

The reaction should be evaluated 10 minutes after testing. It is considered positive if the patient shows a wheal and reports itching at the site of provocation at 36 g/mm² (353 kPa) or less. A wheal response without itching on provocation at 60 g/mm² (589 kPa) or higher indicates the less clinically significant simple dermatographism.¹⁸

Table 4

Specific examinations for diagnosis of urticaria subtypes. All examinations should be performed based on careful history taking and general physical examinations

Subtypes of Urticaria	Types of Examinations	Aims of Examination	Notes
Acute spontaneous urticaria	Blood examinations	To look for possible underlying causes, such as infections	Not mandatory. CBC, CRP and other serum biochemical tests, as necessary, based on the detailed medical history and physical examinations
Chronic spontaneous urticaria	Blood examinations	To look for possible underlying causes, such as infections, thyroid autoimmunity, autoinflammatory diseases	Not mandatory. CBC, CRP and other serum biochemical tests, as necessary, based on the detailed medical history and physical examinations. Thyroid functions and antithyroid autoantibodies may be examined for thyroid autoimmunity. Increase of monoclonal IgM or IgG in addition to recurrent bouts of unexplained fever and pain in the joints, muscles, and/or bones suggest Schnitzler syndrome
		To evaluate disease severity/activity	D-dimer, FDP, prothrombin fragment F1+2, CRP, and serum levels of several proinflammatory cytokines may reflect disease severity and/or activity, but their sensitivities are low. ^{7,8} Peripheral blood basopenia and low release of histamine from basophils may also be associated with disease activity ^{9,10}
	Autologous serum skin test (ASST)	Screening of histamine-releasing autoantibodies against IgE or the high-affinity IgE receptor (FcεRI)	The presence of functional and specific autoantibodies may be verified by a positive bioassay using basophils (the histamine release assay or cell surface expression of activation marker) and a positive immunoassay (Western blotting or ELISA). ¹¹ A protocol for ASST is shown in Fig. 4. ¹²
	Skin biopsy	To differentiate from other diseases, such as urticarial vasculitis and erythema multiforme	Histopathology of urticaria lesions typically shows edema of the upper and mid dermis and dilatation of the postcapillary venules and lymphatic vessels. A small to intermediate infiltration of lymphocytes with or without granulocytes around small blood vessels and edema is commonly observed in the upper dermis. Histopathology does not show interface dermatitis observed in erythema multiforme, or apparent leukocytoclastic vasculitis observed in Schönlein-Henoch purpura and urticarial vasculitis
	Provocation and elimination test	To test the involvement of dietary pseudoallergens	For a diagnosis of food pseudoallergy, a 3-week pseudoallergen-free diet is recommended ¹³

(continued on next page)

Table 4
(continued)

Subtypes of Urticaria	Types of Examinations	Aims of Examination	Notes
Cold contact urticaria	Provocation test	To confirm the diagnosis by testing skin reactivity for low temperature	Ice cube, cool packs, cold water, or special instruments may be applied on the volar forearm for 5 min. Thresholds may be determined by temperature and/or time of provocation
	Blood examinations	To rule out the involvement of cryoprotein	Plasma cryoglobulin may be measured to rule out cryoglobulinemia as an underlying cause
Delayed pressure urticaria	Provocation test	To confirm the diagnosis by testing skin reactivity for physical pressure	A weight bag or special instruments may be loaded on the shoulder, upper back, thighs, or volar forearm. Thresholds may be determined by the level of pressure (area and weight) and/or time of provocation
	Skin biopsy		In addition to changes observed in other subtypes of urticaria, moderate infiltrations of eosinophils and upregulation of several adhesion molecules may be observed in the mid to lower dermis
Heat contact urticaria	Provocation test	To confirm the diagnosis by testing skin reactivity for high temperature	Metal or glass cylinders filled with hot water, or special instruments may be loaded on the volar forearm for 5 min. Thresholds may be determined by temperature and/or time of provocation
Solar urticaria		To confirm the diagnosis by testing skin reactivity for sunlight	Sunlight, solar simulators with filters, or a monochromator may be irradiated to the buttock area. Thresholds may be determined by the time of provocation. The specific wavelength for provocation may be determined. The suppressive wavelength may also be determined in some patients
Urticaria factitia/ dermographic urticaria/ mechanical urticaria		To confirm the diagnosis by testing skin reactivity for scratching or shear forces	A smooth blunt object, such as the tip of a closed ball point pen or a wooden spatula, or special instruments may be applied on the volar forearm or upper back. Thresholds may be determined by the level of pressure using a special instrument
Vibratory urticaria/ angioedema		To confirm the diagnosis by testing skin reactivity for vibration	The volar forearm may be attached to a laboratory vortex mixer for 10 min at 1000 rpm
Aquagenic urticaria	Provocation test	To confirm the diagnosis by testing skin reactivity for contact with water	Attaching compresses with water or 5% saline on the back or volar forearm at body temperature for 20 min. Wiping the test area with an organic solvent such as acetone may increase the reactivity

Cholinergic urticaria	Provocation test	To confirm the diagnosis by testing skin reactivity for sweating	Perform an appropriate physical exercise to the point of sweating and up to 15 min beyond (eg, on a treadmill or stationary bicycle). The age and general condition of the patient should be considered before exercising. Wearing warm clothing in a warm room facilitates the provocation tests
	Skin test	To test the increase in reactivity to acetylcholine	Wheal and flare with satellite wheal formation in response to 20 µg or less of acetylcholine in 20 µL of saline injected into the dermis are evaluated as positive. Only one-third to one-half of patients show positive reactions ^{14,15}
Adrenergic urticaria	Skin test	To confirm the diagnosis by testing skin reactivity for adrenaline	Wheal and flare with a halo of blanched skin in response to 10–20 ng of noradrenaline or 5 ng of adrenaline in 20 µL of saline injected into the dermis are evaluated as positive
Contact urticaria	Skin test	To confirm the diagnosis by testing skin reactivity for a suspected substance	Open test with original or adequately diluted suspected substance should be taken first. Prick test may be performed if the open test is negative. An intradermal skin test may be performed only for limited cases when strongly suspected from the history and the other skin tests are negative
Exercise-induced anaphylaxis/urticaria	Provocation test	To confirm the diagnosis by testing sensitivity to exercise, certain foods, and their combinations in vivo	Exercise should be undertaken in a controlled setting, such as the Bruce method, ¹⁶ with a continuous cardiac monitor and emergency equipment. For the diagnosis of food-dependent exercise-induced anaphylaxis, both exercise and food challenges are taken separately and in combination. If both challenges are negative, 100–500 mg of aspirin may be added for provocation ¹⁶
	Tests for type I allergy	To confirm the sensitivity against a suspected food antigen	General examinations for type I allergy: binding of circulating IgE, such as ImmunoCAP, the prick test, and the basophil activating test. In case of wheat-dependent exercise-induced anaphylaxis, detection of serum IgE against ω-5 gliadin is valuable ¹⁷
Urticaria evoked by particular substances	Tests for type I allergy	To confirm the sensitivity against a suspected food antigen	General examinations for type I allergy: binding of circulating IgE, such as ImmunoCAP, the prick test, and the basophil activating test
	Provocation test	To confirm the diagnosis by testing local skin or whole body reactivity for a suspected substance	Challenge with suspected substances. Tests should begin with a small amount of suspected substance to avoid serious reactions, such as anaphylactic shock. No reliable in vitro test is available for nonallergic anaphylactic reactions, such as NSAID-induced urticaria/anaphylaxis
Angioedema	Blood test	To determine the involvement of C1-INH	C3, C4, CH50, C1-INH (amount of protein and activity), C1q
	Gene analysis	To determine the presence or absence of a gene disorder in C1-INH and/or factor XII	Gene sequences for C1-INH and/or factor XII

All provocation tests and skin tests should be performed without the effect of medications. Antihistamines should be discontinued for at least 2 to 3 days.

Abbreviations: C1-INH, C1-inhibitor; CBC, complete blood count; CRP, C-reactive protein; ELISA, enzyme-linked immunosorbent assay; FDP, fibrin degradation products.

Cold contact urticaria/acquired cold urticaria

Symptoms of cold contact urticaria appear on exposure of the skin to cold fluids or cold surfaces. Provocation testing should be performed by applying a cold stimulus to the skin of a volar forearm, abdomen, or a hand. The stimulus may be a melting ice cube with a thin plastic bag, a cool pack, or a cold water bath. If the skin is directly in contact with water, symptoms due to aquagenic urticaria should be differentiated. Ice cube testing should be performed for 5 minutes. The time of contact may be shortened if the patient's history suggests that the patient is very sensitive and may develop massive reactions. If patients do not develop wheals after provocation for 5 minutes, the ice cube may be applied for up to 20 minutes. Patients may be tested further by immersing an arm in cold water at 5 to 10°C for 10 minutes. Test sites should be assessed 10 minutes after the end of the provocation step.¹⁸

The test should be considered positive if the skin site exposed to the cold shows a palpable and clearly visible wheal and flare. A special instrument, *Temp Test 3.0* (EMO Systems GmbH, Berlin, Germany), developed for the diagnostic evaluation of cold contact urticaria, may be used to determine the threshold, in addition to making a diagnosis.²²

Delayed pressure urticaria

Patients with this subtype of urticaria develop a skin swelling on the site of sustained pressure often with pain or burning sensations with or without itching. Whealing occurs after a latent period, typically 2 to 4 hours after the pressure stimulus has been applied. The resulting swelling is deep and large compared with most other urticaria subtypes. Moreover, unlike angioedema, this urticaria subtype is not associated with mucosal symptoms.¹⁹ Skin biopsies reveal an inflammatory infiltrate with prominent eosinophils, but no vasculitis. Provocation may be performed by suspending a 7 kg weight on a 3 cm shoulder strap for 15 minutes, or applying rods supported in a frame to the back, thighs, or forearm, or using a calibrated dermatographometer on the upper back. Regarding rod weight application, Lawlor and colleagues²³ used a 1.5-cm diameter rod with a weight of 2.29 kg (127 kPa) to 4.79 kg (266 kPa) for up to 15 minutes on the back. Barlow and colleagues²⁴ used 1.5-cm diameter rods with 2.5 kg (139 kPa) and 3.5 kg (194 kPa) for 20 minutes on the anterior thighs. In our clinical practice, we use a 1.4-cm diameter rod with a weight of 4.0 kg (255 kPa) for 15 minutes on the back (Fig. 1).²⁵ The approach recommended by a EAACI/GA²LEN/UNEV panel is to apply a 2.5-kg weight with a 1.5-cm diameter rod, or a 5-kg weight with 6.5-cm diameter rod for 15 minutes.¹⁸ When using a dermatographometer, the device should be applied at 100 g/m² (981 kPa) for 70 seconds on the upper back.^{18,26}

Heat contact urticaria

Heat contact urticaria is rare and is characterized by the appearance of a wheal and flare on the skin area locally heated to a certain temperature. Provocation is performed by applying hot metal or glass cylinders filled with hot water to the skin of the volar forearm. The *Temp Test* described for cold contact urticaria may also be used for this type of urticaria.²² The temperature for provocation should be 45°C, but may be higher. A standard time for provocation is 5 minutes, but shorter or longer times may be appropriate in some patients.¹⁸ The area exposed to heat should be inspected 10 minutes after the provocation. The test should be considered positive if the test site shows a palpable and clearly visible wheal-and-flare type skin reaction.¹⁸

Solar urticaria

Wheal-and-flare reactions of solar urticaria appear in response to the exposure of skin to sunlight. Ideally, provocation testing should be done on the buttock skin, but the

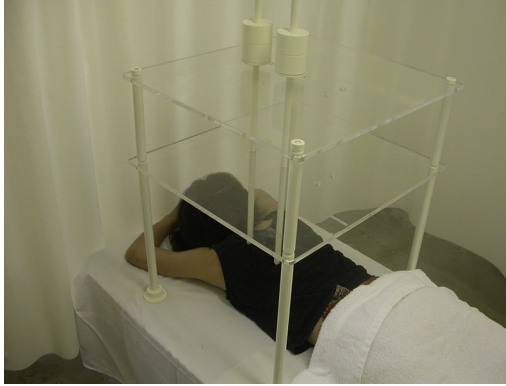


Fig. 1. Device for a pressure challenge test (4 kg/1.5 cm², for 15 minutes). (Adapted from Morioke S, Takahagi S, Iwamoto K, et al. Pressure challenge test and histopathological inspections for 17 Japanese cases with clinically diagnosed delayed pressure urticaria. Arch Dermatol Res 2010;302:614; with permission.)

parts of the trunk that are usually covered by clothes can also be tested (**Fig. 2**). The light source may be sunlight or a slide projector from 10 cm distance with or without filters, or a monochromator (UV-A, UV-B, visible light).^{18,27} The test site should be inspected 10 minutes after the irradiation. The provocation time may be shortened or prolonged based on the severity of the symptoms predicted by the patient's history.

The action wavelength spectrum of each patient may be determined by using either light filters or monochromator(s). In some patients, the development of a wheal by an action wavelength may be suppressed by exposure to other wavelengths.²⁸ Patients with solar urticaria reported from Europe and North America tend to be sensitive to ultraviolet part of the spectrum rather than visible part of the spectrum, whereas patients from Japan and Singapore tend to be more sensitive to visible light than ultraviolet light (**Fig. 3**).^{14,27-32}

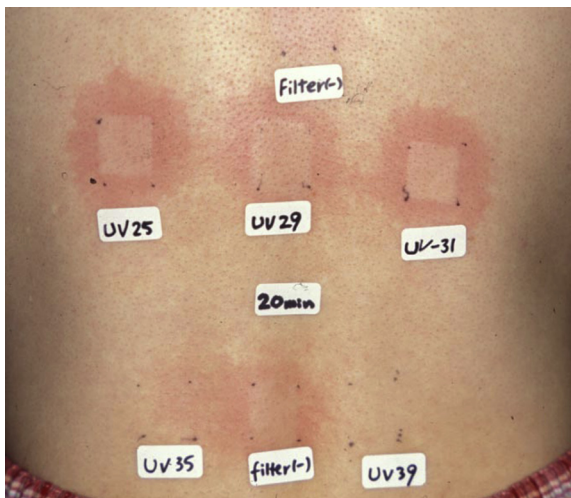


Fig. 2. Wheal-and-flare reactions in response to light irradiated from a slide projector through various filters. (Adapted from Kawai M, Hide M, Okabe T, et al. A case of solar urticaria induced by UVA. Nishinihon J Dermatol 2000;62:299; with permission.)

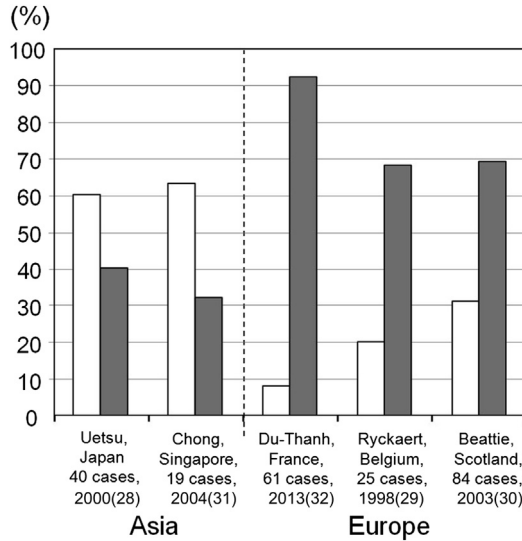


Fig. 3. Action wavelengths for patients with solar urticaria reported in various countries. Patients with solar urticaria reported in Japan and Singapore are more susceptible to visible light than to ultraviolet light, whereas the pattern is the other way round for patients in Europe. Open bar, sensitive to visible light only; filled bar, sensitive to ultraviolet light.

Vibratory urticaria/angioedema

Vibratory urticaria/angioedema is characterized by itching and swelling of the skin exposed to vibration. For provocation, the forearm is held on a flat plate placed on a vortex mixer that is run at between 780 rpm and 1380 rpm for 10 minutes. The site of application should be assessed for swelling 10 minutes after testing. The measurement of the circumference of the arm before and after the provocation at 3 points (wrist, midforearm, and elbow) can help with evaluation of swelling.¹⁸

Aquagenic Urticaria

Aquagenic urticaria is a relatively rare subtype of urticaria, characterized by small follicular wheals and flare on exposure to aqueous solutions. Provocation is performed by attaching wet cloths at body temperature for 20 minutes.¹⁸ Wiping the test area with an organic solvent, such as acetone or ethanol, and challenging with saline instead of tap water may increase the reactivity (Fig. 4).³³

Cholinergic Urticaria

Cholinergic urticaria is a subtype of urticaria common in children and young adults.³⁴ Symptoms of cholinergic urticaria develop in conditions causing sweating, such as exercise, taking a hot bath, or emotional stimuli.¹⁸ It may be accompanied by angioedema and systemic symptoms including wheezing or, rarely, anaphylaxis. Cholinergic urticaria must be differentiated from exercise-induced urticaria/anaphylaxis, which is induced by exercise but not by passive warming. The diagnosis is established by an appropriate provocation test and/or skin test with acetylcholine.^{14,15,18}

Provocation is performed by physical exercise appropriate for the patient's age and general condition (eg, on a treadmill or stationary bicycle). The exercise should be performed to the point of sweating and up to 15 minutes beyond this point. To differentiate from exercise-induced anaphylaxis, a passive warming test should be done,

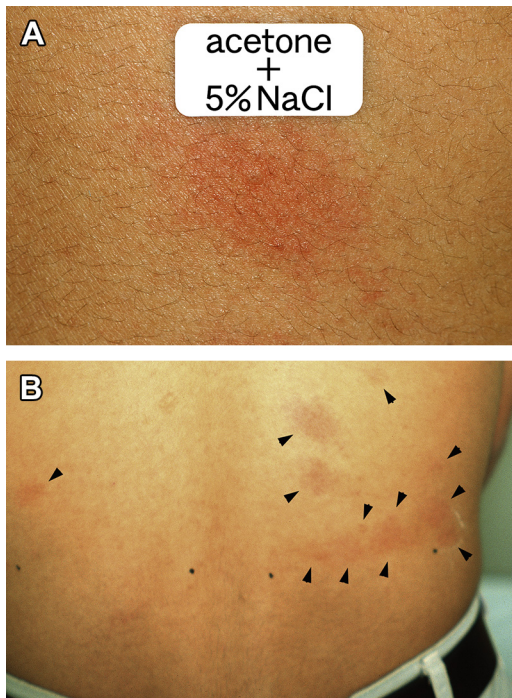


Fig. 4. Wheal-and-flare reactions induced by contact with 5% saline on the back for 15 minutes. (A) A wheal with flare appeared at a hair follicle. (B) Pretreatment with acetone induced more wheals and flares indicated by *arrowheads* (right) than in the control (left). (From Hide M, Yamamura Y, Sanada S, et al. Aquagenic urticaria: a case report. *Acta Derm Venereol* 2000;80:148; with permission.)

recording core body temperature to achieve an increase of 1.0°C or more. The skin should be inspected immediately and 10 minutes after the end of the test.¹⁸

Skin testing with intradermal injection of 0.1 mL of acetylcholine at 100 µg/mL may reinforce the diagnosis of cholinergic urticaria (Fig. 5). The test should be considered positive if the test site shows satellite wheals around the injection site. The specificity of this test seems to be high, but the sensitivity is approximately 30% to 50%.^{14,15}

Adrenergic Urticaria

Adrenergic urticaria has been reported to be a rare subtype of urticaria. Patients develop small maculopapular lesions with a halo of blanched skin in association with psychological tension.^{35–39} Wheal and flare may be reproduced by a skin test with 5 ng of adrenaline or 10 to 20 ng of noradrenaline in 20 µL of saline (Fig. 6). Although the independence of this disease entity is controversial, symptoms improved in all cases treated with propranolol reported so far.^{35–39}

Contact Urticaria

Contact urticaria (see the article by McFadden in this issue for a detailed review) is characterized by immediate development of a wheal and flare with itching at the site of contact with specific substances and may be immunologic (IgE-mediated) or less commonly nonimmunologic. The wheal and flare usually appears within



Fig. 5. Wheal-and-flare reactions induced by intradermal injections of 20 µL of acetylcholine at 10 µg/mL and 100 µg/mL.

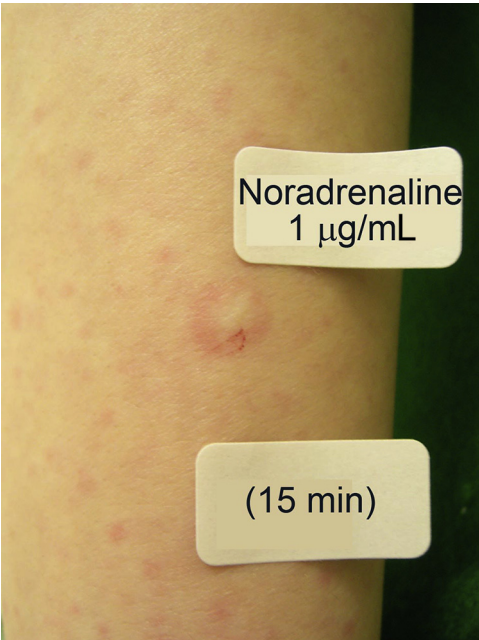


Fig. 6. A pale wheal and surrounding flare induce by injection of 20 µL of noradrenaline at 1 µg/mL.

30 minutes and completely disappears within a few hours and may also develop into generalized urticaria and even anaphylaxis.⁴⁰

The suspected substance is applied in its original form or as an extract on a normal-looking 3 × 3 cm area of the volar forearm or the upper back for 15 to 20 minutes.⁴⁰ The EAACI/GA²LEN/EDF/UNEV consensus panel recommends reading the reaction 20 minutes after the provocation (open test).¹⁸ If this test is negative, the next step is occlusive application. We use chambers for closed patch testing for this purpose. For patients with a history of severe symptoms, tests should be started with sufficiently diluted suspected substances. If no itchy wheal and flare appears in these tests, a prick test may be performed.^{40,41} The performance of intradermal skin tests should be limited to patients for whom contact urticaria is strongly suggested by the history but negative results are obtained for both the open test and the skin prick test. In vitro tests may also be used for contact urticaria by type I allergy, such as latex allergy.⁴⁰

Exercise-Induced Anaphylaxis/Urticaria

Exercise may result in anaphylaxis with an urticarial eruption in patients with this category. Some patients may develop urticaria and anaphylaxis regardless of food intake (EIA), but other patients develop anaphylaxis only when they exercise after partaking of a food (FDEIA). The diagnosis of EIA and FDEIA is based on the detailed history and adequate provocation testing performed as necessary. The demonstration of specific food allergen-reactive IgE in the serum may help, but may not be sufficient for the diagnosis of FDEIA in some cases. Some patients may develop anaphylaxis by exercise after intake of any food but, in others, IgE-mediated allergy to 1 or more specific food allergens is involved.⁴² The presence of anti- ω 5-gliadin IgE in adults has been reported to be an exceptionally good marker for FDEIA caused by wheat with regard to sensitivity and specificity.¹⁶

The exercise challenge test is typically performed according to the protocol of Bruce and colleagues⁴³ with a continuous cardiac monitor and emergency equipment. In cases of FDEIA, the provocation test should include the food challenge alone, exercise alone, and a combination of food ingestion and exercise. The amounts of food and exercise required to cause symptoms to develop are largely variable not only among patients but also vary depending on the different circumstances in which the same patient is tested. Other conditions, such as fatigue, lack of sleep, or low temperature may affect the threshold for developing anaphylaxis.¹⁷ Aspirin intake is a well-documented augmenting factor for FDEIA. To provoke or exacerbate symptoms, 500 mg of aspirin may be taken together with the suspected food.⁴⁴ In some cases, the combination of only aspirin and a culprit diet may result in anaphylaxis.⁴⁵ The sensitivity of provocation testing for FDEIA was reported to be up to 70%.¹⁶

Urticaria Induced by Particular Substances

Acute urticaria may develop in response to the intake of particular substances as a result of a specific hypersensitivity. The mechanism could be either type I IgE-mediated or nonimmunologic. In cases of type I allergy, hypersensitivities of individual patients should be proved by serum tests, such as ImmunoCAP, and IMMULITE 3gAllergy or basophil activating tests (BAT), such as the histamine release test and CD203c expression on the surface of basophils, or skin testing, such as the prick test as described earlier.^{16,17,46} In cases of urticaria induced by nonimmunologic mechanisms, such as those from radiographic contrast media or nonsteroidal antiinflammatory drugs (NSAIDs), provocation is the only examination for a definitive diagnosis. The provocation test may be appropriate in selected patients and should begin with sufficiently small

amounts of suspected substances under careful observation and with emergency equipment readily available.

Angioedema

Angioedema is a common complicating feature of some subtypes of urticaria and, like urticaria, is usually taken to be mast cell mediated. Cases where angioedema appears by itself may also be mast cell mediated. However, a bradykinin-mediated mechanism should be excluded. It is important to ask patients if they use an angiotensin-converting enzyme inhibitor, which inhibits bradykinin degradation and may elicit bradykinin-mediated angioedema. Hereditary angioedema cannot be ruled out if the patient developed the first symptoms of angioedema by adolescence, and/or a sibling has the same condition. For the screening of bradykinin-mediated angioedema, blood levels of C3, C4, C1-inhibitor (C1-INH) (protein concentration and activity), and C1q are informative. If an acquired form of C1-INH is suspected, lymphoproliferative diseases should be ruled out (see [Tables 2](#) and [4](#)).⁶

DIAGNOSIS OF UNDERLYING CAUSES OR DISEASES

Several factors, diseases, and/or conditions have been reported as underlying causes of urticaria. Frequently suspected factors in relation to spontaneous urticaria are listed in [Box 1](#). However, a systematic review of the laboratory investigations for chronic urticaria revealed that the number of diagnoses identified varied from 1% to 84%, and was not related to the number of laboratory tests performed.⁴⁷ Therefore, intensive programs of clinical examinations are not recommended for routine screening of the causes of urticarias, unless suggested by the medical history and/or physical examination.^{1,4,47}

Infections

Acute infections by viruses and bacteria are known to be often associated with the onset of acute urticaria and transient aggravation of chronic spontaneous urticaria. Many studies have suggested chronic persistent infection by *Helicobacter pylori* as an important cause of chronic spontaneous urticaria. However, its significance is disputed.^{1,4,48} The relationship between many other kinds of infections and urticaria have not been substantiated.

Stress and Fatigue

Many investigators have suggested a relationship between stress and/or fatigue and aggravation and/or elicitation of urticaria.^{4,48} However, urticaria itself induces stress and impairs the quality of life of patients.^{49,50} Therefore, it is largely controversial if stress and fatigue should be included as underlying causes of urticaria. Moreover,

Box 1 Factors suggested as underlying causes of urticaria 1. Infection (acute, chronic) 2. Stress, fatigue 3. Autoimmunity against thyroid 4. Autoimmunity against IgE/FcεRI 5. Pseudoallergy (food, drug) 6. Other organ disorders

no diagnostic test for these factors has been established. Nevertheless, with respect to quality of life assessments, it is good clinical practice to ask patients with urticaria about their psychosomatic and psychiatric conditions.

Autoimmunity Against the Thyroid

Autoantibodies against thyroglobulin, thyroid microsomal antigen, and thyroid peroxidase may be detected in patients with chronic spontaneous urticaria, regardless of an apparent disorder of thyroid function.^{51–53} However, results from recent studies conducted on a large scale do not support the therapeutic effect of thyroxine on urticaria.^{54,55}

Autoimmunity Against IgE/High-Affinity IgE Receptor (FcεRI)

Approximately 30% to 50% of patients with chronic spontaneous urticaria have IgG autoantibodies that activate mast cells and basophils by crosslinking of IgE and/or the high-affinity IgE receptor (FcεRI).^{19,56,57} The presence of such autoantibodies should be demonstrated by a histamine release assay using the patient's serum and basophils from healthy donors.^{56,57} However, this assay is somewhat cumbersome and requires special equipment, which has therefore limited its application across the world. A solid phase assay, such as enzyme-linked immunosorbent assay, is relatively easy and quantitative, but not specific.¹¹ Alternatively, skin reactions evoked by intradermal injection of autologous serum (autologous serum skin test [ASST]) have been widely used as a screening test because of their relative simplicity and high sensitivity.^{11,12,58,59} So far, various modifications of the ASST have been made but its specificity has not been solidly established for use in clinical practice. The EAACI task force reviewed the evidence regarding ASST for best practice for chronic spontaneous urticaria in 2009 and 2013.^{11,12} Their recommended procedure for ASST is shown in **Fig. 7**.

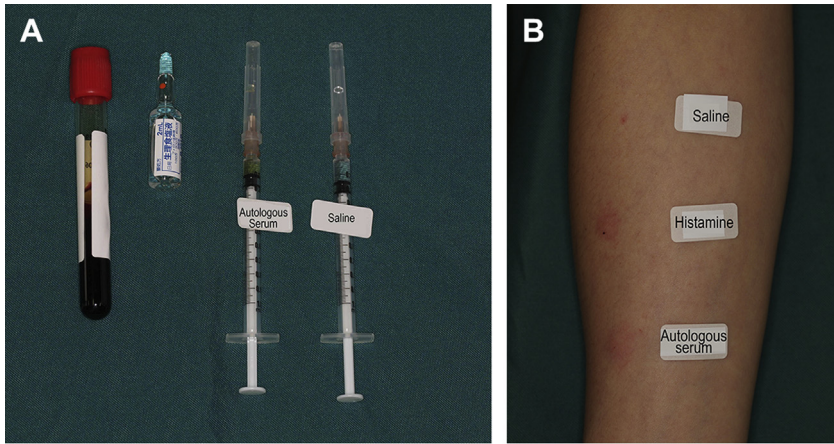
The ASST should be performed at least 2 to 3 days after the last dose of H1 antihistamine. Patients should have also ceased using systemic corticosteroids, equivalent to or more than 15 mg prednisolone, heparin and antileukotrienes before performing the ASST. Standard precautions for handling blood products are required to protect both the patient and the operator.¹²

Pseudoallergy

Nonallergic hypersensitivity to dietary pseudoallergens, including naturally occurring food ingredients, such as salicylates and biogenous amines, food additives, and continuous use of oral or topical NSAIDs may be relevant as a cause and/or precipitating or aggravating factor for chronic spontaneous urticaria. Because the mechanism of pseudoallergen provocation of urticaria remains unclear, strict exclusion and subsequent provocation testing with a suspected substance are necessary for the diagnosis.¹³ For a diagnosis of food pseudoallergy, a 3-weeks pseudoallergen-free diet is recommended.¹³

Other Organ Disorders

Many diseases or disorders, including malignancies, have been reported to underlie spontaneous urticaria. In some cases, the treatment of these disorders resulted in the remission of the urticaria. With respect to physical urticaria, cryoglobulinemia was identified in several patients with cold contact urticaria.^{18,60} However, in other cases, the relationship between these disorders and the pathogenesis of urticaria is largely unknown. Moreover, screening for malignant neoplasms as a routine in urticaria is no longer recommended, because the incidence of neoplasms in patients



C

Collect blood into sterile (no additive) glass tubes without additives.

(Red-topped 7 mL BD Vacutainer® [Becton, Dickinson and Company, Franklin Lakes, NJ, USA] blood collection tubes is recommended)



Allow blood to clot at room temperature for 30 min.

Centrifuge sample at 450-500 g for 10 min.



Clean the volar forearm skin with antiseptic.

Perform intradermal injections of 0.05 mL of normal saline as a negative control and the same amount of autologous serum. Skin prick with 10 mg/mL histamine solution or intradermal injection of 0.05 mL of 0.5 to 1.0 µg histamine as a positive control.



Wait 30 min



Ensure a positive histamine reaction, and measure the two longest perpendicular diameters of any red wheal reactions to the ASST and the normal saline skin test.

Fig. 7. The autologous serum skin test (ASST) and devices for the test. (A) The identity of the blood donor and the labeling of samples should be verified to avoid any risk of skin testing with the wrong serum. (B) Fifty microliters of autologous serum, saline, and 10 µg/mL histamine are injected, respectively. (C) Flowchart for ASST procedure recommended by the EAACI/GA²LEN/EDF/WAO task force. (Adapted from Konstantinou GN, Asero R, Maure M, et al. EAACI/GA(2)LEN task force consensus report: the autologous serum skin test in urticaria. *Allergy* 2009;64:1257 and 1261; with permission.)

with urticaria and that in the general population have been found to be similar.^{1,61} If any symptoms different from urticaria are recognized, clinical examinations should be undertaken as necessary.

EVALUATION OF THE SEVERITY OF URTICARIA

The evaluation of disease severity of inducible urticarias may be performed according to the threshold for eliciting factors. For spontaneous urticarias and angioedema, questionnaire-based scores may be used.^{1,62} The urticaria activity score over 7 consecutive days (UAS7) is a unified and simple scoring system, validated in comparison with the Dermatology Life Quality Index (DLQI).⁶³ The quality of life of patients with

superficial urticaria and that of patients with angioedema may be evaluated using the Chronic Urticaria Quality of Life Questionnaire (CU-Q2oL)⁵⁰ and Angioedema Quality of Life Questionnaire (AE-QoL),⁶⁴ respectively.

Coagulation/fibrinolysis markers, such as D-dimer, fibrin degradation products, prothrombin fragment F1+2, and C-reactive protein have been reported to reflect disease severity and/or activity, but their sensitivities are low.^{7,65} Serum levels of proinflammatory cytokines, such as interleukin (IL)-6, tumor necrosis factor (TNF), and IL-23, may also reflect disease activity in certain patients,^{7,66} but are of doubtful usefulness.⁸ Peripheral blood basopenia and low release of histamine from basophils may also be associated with disease activity,^{9,10} but their value is at present confined to the research laboratory.

SUMMARY

Diagnostic tests for urticaria should be performed based on the detailed history of the patient and physical examination. The definitive diagnosis of urticaria subtypes, which may be complicated in the individual patient, is important for both adequate treatment and further detailed examinations specific for individual subtypes. Disease severity and activity of spontaneous urticaria and angioedema are evaluated by questionnaire-based scoring systems. The establishment of more sensitive and specific biomarkers is a major aspiration in the future management of spontaneous urticaria and angioedema.

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