# Urticaria: A comprehensive review

## Epidemiology, diagnosis, and work-up

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**Learning objectives**
After completing this learning activity participants should be able to recognize the various type of urticaria; recall diagnostic strategies for confirming the diagnosis; and describe the key histopathology features involved in the diagnosis of urticaria.

**Disclosures**
**Editors**
The editors involved with this CME activity and all content validation/peer reviewers of the journal-based CME activity have reported no relevant financial relationships with commercial interest(s).

**Authors**
The authors involved with this journal-based CME activity have reported no relevant financial relationships with commercial interest(s).

**Planners**
The planners involved with this journal-based CME activity have reported no relevant financial relationships with commercial interest(s). The editorial and education staff involved with this journal-based CME activity have reported no relevant financial relationships with commercial interest(s).

Urticaria is a common clinical condition presenting with wheals (hives), angioedema, or both. Urticaria has a complex pathogenesis, along with a high disease burden, a significant impact on quality of life, and high health care costs. The first article in this continuing medical education series covers the definition, classification, epidemiology, diagnosis, and work-up of urticaria, taking into account the recent literature and the best available evidence. (J Am Acad Dermatol 2018;79:599-614.)

***Key words:*** acute; angioedema; chronic physical urticaria; histopathology; hives; inducible urticaria; testing; urticaria; wheals.

Urticaria presents with wheals (hives), angioedema, or both, and has a lifetime prevalence of about 9%.[1,2] The appearance of pruritic, erythematous dermal swellings that blanch with pressure, indicating the presence of vasodilation and superficial dermal edema, is characteristic of wheals.[3] Angioedema is caused by similar pathologic alterations that occur in the reticular dermis and subcutaneous tissue, with poorly defined swelling and burning.[4] One-third of patients present with both hives and angioedema, 30% to 40% present with isolated hives, and 10% to 20% with isolated angioedema.[1,5,6]

*Abbreviations used:*

| | |
|---|---|
| ASST: | autologous serum skin test |
| AU: | acute urticaria |
| CSU: | chronic spontaneous urticaria |
| CsA: | cyclosporine |
| CU: | chronic urticaria |
| DPU: | delayed pressure urticaria |
| NSAID: | nonsteroidal antiinflammatory drug |

The spinothalamic tract is thought to play an important role in the pathway of pruritus.[7] Primary afferent neurons, also known as pruriceptors, detect itch-inducing substances like histamine and chloroquine.[8] The most well-known pruritogen is

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Funding sources: None.
Conflicts of interest: None disclosed.
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0190-9622/$36.00

https://doi.org/10.1016/j.jaad.2018.01.020
**Date of release: October 2018**
**Expiration date: October 2021**

histamine; however, non-histaminergic mediators also exist.[9] Initially it was thought that the nerve fibers only responded to histamine/nonhistamine stimulus, but it is now accepted that these fibers can also be stimulated by noxious stimuli.[7]

Urticaria has a complex pathogenesis and a significant impact on quality of life.[1,10] Urticaria-related costs may be as high as $1750 to $2050 per patient per year.[11,12]

## CLASSIFICATION

### Key points

- **Urticaria cases are classified as either acute or chronic**
- **Chronic urticaria is defined if daily or almost daily wheals or angioedema are present for >6 weeks**

Urticaria can be classified according to duration and etiology,[13] although ≥2 types of urticaria can coexist in the same patient (Table I).

**Table I.** Classification of urticarias*

| Type | Clinical feature or type |
|---|---|
| Acute urticaria | |
| Chronic urticaria | |
| Chronic spontaneous urticaria | Spontaneous appearance of itchy wheals, angioedema, or both for ≥6 weeks because of known† or unknown causes |
| 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 |

*Modified from data presented by Zuberbier et al[13] and Margerl et al.[14]
†For example, autoreactivity; that is, the presence of histamine-releasing autoantibodies (also called urticaria factitia).
‡Dermographic urticarial.
§Cold contact urticarial.
¶Pressure urticarial.
#Heat contact urticaria.

## ACUTE URTICARIA

### Key points

- **Acute urticaria has precipitating factors in <50% of cases**
- **When present, the most common triggers are infections, drug reactions, and food intolerance**

Acute urticaria (AU) is defined by the occurrence of spontaneous wheals or angioedema for <6 weeks.[13] In acute cases, it is important to exclude anaphylaxis in the presence of respiratory, gastrointestinal, or neurologic symptoms or hemodynamic instability.

Eliciting factors have been found in <50% of cases, with upper respiratory infections being the most common trigger (40%), followed by drug reactions (9.2%) and suspected food intolerance (0.9%).[15] Among infectious agents, upper respiratory tract agents, *Mycoplasma pneumonia*, and parasitic infections have been commonly reported in children,[16] while viral hepatitis and infectious mononucleosis are important culprits in adults.[17-19]

## CHRONIC URTICARIA

### Key points

- **Chronic urticaria may be subclassified into chronic spontaneous urticaria or chronic inducible urticaria**
- **Up to 30% of cases are associated with functional immunoglobulin G antibodies to the high-affinity immunoglobulin E receptor FcεRIα or to immunoglobulin A**
- **Among patients in which an etiology is suspected, infections, drugs, food, and psychological factors are the most commonly associated**
- **Chronic inducible urticaria is characterized by its ability to be triggered consistently and reproducibly in response to a specific stimulus**

Episodes of daily or almost daily wheals or angioedema lasting for ≥6 weeks are designated as chronic urticaria (CU).[13,20] CU must be distinguished from acute intermittent urticaria/angioedema, where episodes only last hours or days but recur over months or years.[21]

Chronic inducible urticaria (CIndU) represents a subgroup of CU where urticaria is induced by a determined stimulus rather than occurring spontaneously. If no inducible factor is present, the process is termed chronic spontaneous urticaria (CSU). Among this subgroup, 30% to 40% of patients present with autoantibodies, suggesting an autoimmune basis. These cases would be categorized as chronic autoimmune urticaria (CaU) (European guidelines) or as antibody-associated CU (US guidelines).[22]

**Table II.** Comparison of the recommendations of the EAACI/GA2LEN/EDF/WAO international guidelines and the US practice parameters for confirming the subtypes of chronic inducible urticaria

| Subtype | EAACI/GA2LEN/EDF/WAO international guidelines[14] | Joint Task Force on Practice Parameters[22] |
|---|---|---|
| Aquagenic | Wet cloth at body temperature applied for 20 min | Water compress at 35°C applied to the skin of the upper body for 30 min |
| Cholinergic | Exercise and hot bath provocation | Provocative challenges that raise core body temperature (exercise and hot water immersion 42°C or methacholine intradermal challenge) |
| Cold | Cold provocation and threshold test (ice cube, cold water, and cold wind). Extended diagnostics based on history: CBC with differential, ESR, CRP, or cryoproteins | Cold stimulus (eg, an ice cube on the forearm for 5 min) applied and observe for wheal-and-flare reaction during rewarming of the skin |
| Contact | Cutaneous provocation test. Skin tests with immediate readings (eg, prick test) | |
| Delayed pressure | Pressure test and threshold test | Challenge with 15 lbs of weight suspended over the shoulder for 10 or 15 min and monitor for development of delayed angioedema |
| Heat | Heat provocation and threshold test | See cholinergic urticaria |
| Solar | Ultraviolet and visible light of different wavelengths and threshold test. Extended diagnostics based on history: rule out other light-induced dermatoses | Phototesting to various wavelengths of light |
| Dermatographism | Elicit dermatographism and threshold test (dermographometer). Extended diagnostics based on history: CBC with differential, ESR, or CRP | Stroke the skin with a firm object, such as a tongue blade |
| Vibratory angioedema | Vortex | Vortex mixer applied to forearm for 4 min |

*CBC*, Complete blood cell count; *CRP*, C-reactive protein; *EAACI*, European Academy of Allergy and Clinical Immunology; *EDF*, European Dermatology Forum; *ESR*, erythrocyte sedimentation rate; *GA2LEN*, Global Allergy and Asthma European Network; *WAO*, World Allergy Organization.

## CHRONIC SPONTANEOUS URTICARIA

Neither European nor US guidelines recommend extensive laboratory testing. Other testing can be performed based on the patient's history (Table II).[20,22] In cases where an etiology is suspected, infections are the most commonly associated.[1,13]

### Infections

Bacterial, viral, parasitic, or fungal infections have been implicated as underlying causes of CSU.[23-27] The frequency and relevance of infectious etiologies varies according to the patient population and geographic location.[28,29] Such is the case of *Anisakis simplex*, a sea fish nematode that has been linked to recurrent spontaneous urticaria in the Mediterranean.[30]

The relationship of *Helicobacter pylori* and CSU has been proposed, and a protein component has been shown to induce mast cell degranulation.[31] Clinical data are unclear; some studies show an association, while others do not.[32-34] A few studies have shown that Helicobacter eradication may improve CSU, but the verdict is still unclear.[16,35,36]

### Food

Patients frequently associate foods and food additives with symptom onset; however, type I allergy seems to be a rare cause of CSU.[20] Food allergy as a cause may, however, be considered in patients with intermittent symptoms, typically within 1 hour of exposure.[21]

About 20% of CSU patients have positive prick testing to food allergens, the most common being hazelnut, potato, apple, oatmeal, pork, beef, and seafood.[37-39] In <2% of cases, immunoglobulin E (IgE) allergy is confirmed.[1,40,41]

Another condition is alpha-gal anaphylaxis, which occurs after susceptible patients bitten by a

**Table III.** Cutaneous manifestations in aspirin/NSAID-exacerbated diseases

| Disease | Baseline | Clinical features | Proposed mechanism | Cross-reactivity between groups |
|---|---|---|---|---|
| NECD[60,61] | CSU | Exacerbation of hives/angioedema minutes to 4 h after exposure; NECD in 12-30% of patients with CSU | Increased leuokotrienes and PGD2 | Yes |
| NIUA[60,61] | Healthy | Hives/angioedema 1-6 h after exposure | COX-1 inhibition | Yes |
| Immediate hypersensitivity to aspirin or single NSAID[60,61] | Healthy | Urticaria, angioedema, or anaphylaxis, minutes to 1 h after exposure | IgE-mediated | No |

*COX*, cyclooxygenase; *CSU*, chronic spontaneous urticaria; *IgE*, immunoglobulin E; *NECD*, NSAID-exacerbated cutaneous disease; *NIUA*, NSAID-induced urticaria/angioedema; *NSAID*, nonsteroidal antiinflammatory drug; *PGD2*, prostaglandin D2.

tick develop sensitization to galactose-alpha-1,3-galactose, found in milk and red meat, which then causes a delayed reaction manifesting as urticaria and, in severe cases, anaphylaxis.[21,42,43] Most authors have not found pseudoallergens (eg, food additives and some spices) to be the cause of CU, but a few studies have advocated the relevance of food intolerance as a triggering factor of CSU.[35,44-46] Some studies have shown ≤30% resolution 10 to 14 days after removal of pseudoallergens from patients' diets.[45,47]

## Drugs

The most commonly implicated drugs in CU are angiotensin-converting enzyme (ACE) inhibitors and nonsteroidal antiinflammatory drugs (NSAIDs).[48-51]

ACE inhibitor–induced angioedema and urticaria is caused by the nonimmunologic accumulation of bradykinin and other neurokinins.[52] The incidence may be as high as 0.68%, and can occur from weeks to years after treatment is initiated.[53] Risk factors include African American heritage (4-5 times greater than the incidence in white patients), female sex, atopy, and cigarette smoking.[54] In the event of angioedema, the ACE inhibitor must be discontinued.[55] The majority of patients improve significantly after withdrawal of ACE inhibitors, but episodes may persist for several months.[56-58] Management is the same as CU, and recently the bradykinin antagonist icatibant has shown significantly faster resolution of symptoms than standard therapy with corticosteroids and antihistamines.[59]

Table III lists cutaneous manifestations in aspirin/NSAID-exacerbated diseases. NSAID-exacerbated cutaneous disease manifests as exacerbation of symptoms in patients with a history of CSU after intake of an NSAID. NSAID-exacerbated cutaneous disease can be found in 12% to 30% of patients with CSU.[60,61] NSAID-induced urticaria/angioedema, on the other hand, develops in the absence of urticaria history.

In the case of immediate hypersensitivity to aspirin or a single NSAID, symptoms develop rapidly after exposure to the drug.[62] Drugs most commonly implicated include NSAIDs of the pyrazolone class (metimazole), acetic acid (diclofenac), or propionic acid derivatives (ibuprofen).[60]

## Emotional stress

Patients with CSU experience high rates of anxiety, depression, and somatoform disorders, with half being affected by at ≥1 of these conditions.[63] In addition, psychiatric comorbidity appears to be an additional factor in the impairment of quality of life in CSU patients,[21] but it is uncertain if emotional stress/anxiety is the cause or consequence of CSU.[64]

## Chronic autoimmune urticaria (antibody-associated urticaria)

About one-third to one-half of patients with CSU show a positive response against their own serum (positive autologous serum skin test [ASST]).[65] IgG antibodies to the high-affinity IgE receptor FcεRI$\alpha$, or less commonly IgG antibodies to IgE, have been documented.[35,66-69] There seems to be an increased risk for thyroid disorders (hypothyroidism more often than hyperthyroidism), diabetes mellitus type I, systemic lupus erythematous, and rheumatoid arthritis in patients with CaU.[65] Although these autoantibodies are of academic interest, as some studies report a more intense refractory course, their clinical relevance remains unclear.[67,70,71]

There is also an increased frequency of human leukocyte antigen subtypes DRB*04 (DR4) and DQB1*04 (DQ8) among patients with CaU, providing additional evidence of an autoimmune etiology.[72,73]

There is no clear evidence of increased risk of malignancy in CSU,[74] although 1 study did show twice the risk, especially for hematologic neoplasms.[75]

### Chronic inducible urticaria

CIndU is a unique subgroup of CU where patients develop urticaria symptoms exclusively and reproducibly in response to a specific stimulus. Signs and symptoms are usually localized to exposed areas, and with the exception of delayed pressure urticaria (DPU), lesions last <2 hours. It is not uncommon for patients to exhibit multiple CIndU.[14] CIndU is responsible for 20% to 30% of all cases of CU and can be associated with CSU in 14% to 36% of cases.[2,76]

According to the European Academy of Allergy and Clinical Immunology/Global Allergy and Asthma European Network/European Dermatology Forum/Urticaria Network eV consensus from 2016, there are 2 subtypes: physical urticaria (physical trigger) and other inducible urticarias (Table I).[14,77]

CIndUs are diagnosed based on the patient's history and the results of provocation testing (Table IV). CIndU patients may develop systemic signs and symptoms during provocation testing, such as dizziness, vertigo, vomiting/diarrhea, wheezing, and even anaphylactic shock.[14]

### Bradykinin-mediated angioedema

Hereditary angioedema (HAE) and acquired angioedema are bradykinin-mediated vasodilation and increased capillary permeability.[100] HAE types I (85%) and II (15%) are caused by deficient levels of C1 inhibitor or a dysfunctional C1 inhibitor, respectively.[101,102] Patients with HAE type III, on the other hand, have normal C4 and C1-inhibitor levels. These patients are typically females, demonstrate frequent exacerbations with estrogen, and their angioedema is more prominent in the face and oropharynx.[103,104] Contrasting with the hereditary forms, patients with the acquired variant are older at presentation, predominantly male, and have a predilection for the face, but also the abdomen and genitalia.[105-107]

## EPIDEMIOLOGY

### Key points

- **Urticaria is a common worldwide disease**
- **Chronic urticaria develops in 20% to 45% of patients presenting with acute urticaria**
- **Most forms of urticaria are more common in females**

Estimates of the lifetime prevalence for any type of urticaria range from <1% to 24%, depending on the age range, method of sampling, and geographic location.[1,21,108]

AU and CU are more common in women.[109-113] Most studies have found male:female ratios of 1:2, although this difference is less evident in the elderly, children, and for cholinergic urticaria and DPU.[1,11,35,114,115]

The lifetime prevalence of AU ranges from 12% to 24% in Europe.[116-118] Point prevalence ranges from 0.1% to 0.6%.[119,120] CU develops in about 20% to 45% of individuals presenting with AU.[1,111] A study using a large American commercial insurance database found that the 1-year period prevalence for CU was 0.08%,[11] while European data report that the 1-year period prevalence for CU ranges from 0.38% to 0.8%.[1,111,117] The prevalence and incidence for other types of urticaria is lower (eg, the incidence for acquired cold urticaria in Central Europe is approximately 0.05%).[78] Among patients with physical urticaria, the most common type is symptomatic dermographism (40-73%), while solar urticaria, heat urticaria, and vibratory angioedema are more rare.[14,35,121] CU is most common between the ages of 25 and 55 years.[119] In half of patients, the symptoms will be present for <2 years, and in <20% of patients the symptoms last >10 years.[1,110] However, patients suffering from physical urticarias seem to have longer disease processes, with 1 study showing that only 16% were free of symptoms after 1 year.[122]

Urticaria appears to be less common in children than in adults.[123] Urticaria prevalence of any type in children is around 3.4% to 5.4%.[124] The incidence of AU ranges from 2 to 73 per 100,000 emergency department referrals.[116] The prevalence of childhood CU is 0.1% to 0.3% in the United Kingdom.[125]

## ETIOLOGY AND CLINICAL CLASSIFICATION

### Key points

- **Mast cells and basophils are the primary inflammatory cells involved in urticaria pathogenesis**
- **Mast cell activation may be caused by immunologic or nonimmunologic factors. Functional anti-IgE or anti-FcεRIα subunit antibodies are found in ≤50% of patients with CU**
- **Prostaglandin release, rather than histamine mediation, seems to be involved in contact urticaria**

Mast cells and basophils are the major effector cells involved in the development of urticarial lesions.[126] Degranulation releases preformed vasoactive mediators, primarily histamine.[36] Disease

**Table IV.** Characteristics of chronic inducible urticarias

| Type | Subtype | Definition | Subtypes | Incidence | Provocation testing | Comments |
|---|---|---|---|---|---|---|
| Physical urticaria | Symptomatic dermatographism[2,14,77] (dermographic urticaria or urticaria factitial) | Wheals, and in rare cases angioedema, caused by shearing forces on the skin (rubbing, scratching, or scrubbing) | NA | PU is the number 1 cause; 1-5% in the general population | Firm stroke of the skin with a blunt object | Differentiate from simple dermographism or white dermographism |
| | Cold urticaria (acquired cold urticarial or cold contact urticaria)[2,14,77-81] | Rapid onset of itchy wheals after contact cooling and rewarming of the skin | 1. Idiopathic<br>2. Familial<br>a. CAPS<br>b. PLAID<br>3. Acquired | PU is the number 2 cause; up to one-third of all PU cases | Ice cube test | Aquatic activity is a common trigger. Severe cases may lead to anaphylaxis.<br>Counsel patients against swimming |
| | Heat urticaria (heat contact urticaria)[14] | Sudden appearance of itchy wheals after heat contact of the skin | N/A | Exceptionally rare | Hot stimulus to the skin of volar forearm | Differentiate from cholinergic and solar urticaria |
| | Delayed pressure urticaria[14,77,82] | Angioedema occurring after application of a sustained pressure stimulus to the skin | N/A | 37% of patients with CSU | Suspension of weights over the shoulder; application of rods on thigh, or forearm; dermographometer | Develops 6-8 h after, and lasts up to 72 h. Systemic symptoms relatively common (malaise and arthralgia) |
| | Solar urticaria[14,77,83-87] | Development of urticaria within minutes after a brief exposure to sunlight, usually 5-10 min | 1. Type I: abnormal chromophore<br>2. Type II: abnormal circulating IgE antibodies to a normal chomophore | Rare | Provocation phototesting | Chronically light-exposed skin (face and dorsal surface of the hands) is usually resistant |
| | Vibratory angioedema[14,82,88,89] | Itching and swelling, within minutes at the site of skin exposure to vibration | 1. Idiopathic<br>2. Hereditary:<br>- activating mutation ADGRE2 | Very rare | Laboratory vortex mixer | Common triggers: mowing, motorcycle rides, horse riding, or biking; seems to be exaggeration of normal response to dermal vibration |

| | | | | | | |
|---|---|---|---|---|---|---|
| Other inducible urticarias | Cholinergic urticaria (generalized heat urticaria)[14,77,90-92] | Pruritic wheals, angioedema, and or anaphylaxis, precipitated by an increase in core body temperature | 1. Sweat allergy type: hypersensitvity to leaked sweat components, probably antigen secreted by *Malassezia globosa*<br>2. Decreased sweating type: direct effect of acetyl choline in degranulation of mast cells | 5-7% of CU and 30% of CIndU | Moderate physical activity | Triggers: exercise, passive warming, emotional stress, and hot and spicy foods or beverages; numerous, short-lived, tiny wheals surrounded by a large flare reaction |
| | Adrenergic[93-95] | Pruritic wheals after stress-induced released of epinephrine and norepinephrine | N/A | Very rare | Intradermal injection of 5 ng adrenaline or 3-10 ng noradrenaline | Antihistamines are minimally effective. Respond better to beta-blockers like propranolol |
| | Aquagenic urticaria[14,77,78,96,97] | Urticaria after contact with any source of water, independent of temperature | 1. Classic: water as carrier for epidermal antigen<br>2. Salt-dependent aquagenic urticaria: osmotic pressure changes | Very rare | Water compress to skin | Differentiate from aquagenic pruritus, cholinergic urticaria, cold urticaria, and heat urticaria |
| | Contact urticaria[14,98,99] | Development of urticarial lesions, systemic involvement, and in some cases anaphylaxis within minutes after contact to an exogenous agent | 1. NICU: prostaglandin release<br>2. ICU: IgE-mediated hypersensitivity. Requires previous exposure | Variable | Open controlled application testing; skin prick test; closed patch tests | NICU triggers: plants (eg, stinging nettle), animals (eg, jelly fish), or chemicals (eg, cinnamon aldehyde, sorbic acid). ICU triggers: latex, plants, animal products, drugs, cosmetics, and chemicals. Certain occupations seem to be at higher risk (≤90% of cases). Most frequently affected were health care workers, food handlers, hairdressers, and dental assistants |

*CAPS*, Cryopyrin-associated periodic syndromes; *CIndU*, chronic inducible urticaria; *ICU*, immunologic contact urticaria; *NICU*, nonimmunologic contact urticaria; *PLAID*, phospholipase Cγ2 gene–associated antibody deficiency and immune dysregulation; *PU*, physical urticaria.

activity has been correlated with a significant increase in serum C-reactive protein, interleukin-6 (IL-6), IL-6 soluble receptor, and matrix metalloproteinase-9, independent of the presence of a positive ASST or circulating histamine-releasing factors.[123,127] Sleep and circadian rhythm have been implicated in IL-6–mediated processes, and some authors hypothesize that this could be the cause of increased severity of urticaria symptoms at night, when physiological concentrations of IL-6 and IL-6 soluble receptor increase.[128]

### Mast cell–dependent urticaria

Mast cells can be activated by immunologic or nonimmunologic factors. Among the immunologic triggers, IgE-mediated immediate hypersensitivity reaction is the classic mechanism of mast cell activation.[129] This accounts for some cases of acute or episodic urticaria, such as contact urticaria to latex or AU from foods.[130]

IgE is less important in CU, as demonstrated by the lack of correlation between IgE levels and disease severity.[131] CU may also be associated with the presence of functional anti-IgE or anti-FcεRI antibodies in ≤50% of patients.[132] This can be assessed functionally by the ASST. A positive ASST indicates a subset of patients with an increased risk of developing urticaria due to endogenous causes.[133] It has also been found to correlate with disease severity and with patients who have multiple intolerances to NSAIDs.[71] The ASST is the only generally available test to screen for autoantibodies against either IgE or FcεRI.[134] To achieve disease control, these patients might need higher doses of antihistamines or additional immunomodulators. Therefore, this assay is a useful tool in patients who are not responding to traditional therapy. However, the significance of a negative test remains unclear, and some studies have demonstrated low sensitivity of the ASST with a high false-positive rate; therefore, ASST is not a first-line test during the initial work-up.[71] However, the clinical relevance of these antibodies is still unclear, because therapies to treat CU are effective in the presence or absence of these antibodies.

Nonimmunologic mechanisms that can directly activate mast cells include radiocontrast media, opiates, neuropeptides (eg, substance P), and certain foods.[135,136] Reactive oxygen species seem to be another cause of mast cell degranulation; recent evidence suggests that low levels of reactive oxygen species play a role in cell signaling, aiding in the exocytosis of granules content from mast cells.[68,137]

Complement 3a (C3a), C4a, and C5a function as anaphylatoxins by interacting directly with the surface of mast cells to trigger histamine release.[138]

### Mast cell–independent urticaria

There are situations where urticaria does not involve mast cells or histamine.[98] A common example is the development of contact urticaria to sorbic acid, cinnamic acid, cinnamic aldehyde, methyl nicotinate, or dimethyl sulfoxide.[139] These cases do not respond to antihistamines, but rather to acetylsalicylic acid and NSAIDs.[50] It has been proposed that pathogenesis involves prostaglandin release from the epidermis rather than histamine release from mast cells.[98]

### Other mechanisms

Increasing evidence suggests that adipokines such as lipocalin 2 affect immune responses and CU. Lipocalin 2 and urticaria activity have a negative association, suggesting an antiinflammatory effect of lipocalin 2 in CU.[140]

The role of the coagulation pathway in CU came to light when it was found that the autologous plasma skin test had a higher positivity than the ASST.[141] Patients with CU show activation of the extrinsic pathway of the coagulation and fibrinolysis cascade, both of which correlate with disease exacerbation.[142,143]

Together, these findings show the complex pathogenesis of urticaria, beyond simple histamine release or mast cell activation, as previously understood.

## DIAGNOSIS

### Key points

- **Urticaria is characterized by the presence of wheals or angioedema. A detailed history and physical examination are essential in excluding alternative diagnoses and in guiding additional investigations**
- **Individual lesions lasting >24 hours, associated purpura, tender wheals, or the presence of systemic symptoms should prompt further work-up, including obtaining a skin biopsy specimen**

### History and physical examination

A detailed history is essential, and should document the frequency, circumstances of onset, triggers, duration of individual lesions, pattern of recurrence, duration of attacks, whether lesions are itchy or painful, and if episodes are associated with systemic symptoms. Detailed drug and family history, as well as response to treatment, are important. In addition, severity using the urticaria activity score or a visual analogue scale, can be assessed at baseline to use as a gauge for response to treatment.[22]

**Table V.** Recommended history intake*

Pertinent questions

1. Time of onset of disease
2. Frequency/duration of and provoking factors for wheals
3. Diurnal variation
4. Occurrence in relation to weekends, holidays, and foreign travel
5. Shape, size, and distribution of wheals
6. Associated angioedema
7. Associated subjective symptoms of lesions, for example pruritus and pain
8. Family and personal history regarding urticaria or atopy
9. Previous or current allergies, infections, internal diseases, or other possible causes
10. Psychosomatic and psychiatric diseases
11. Surgical implantations and events during surgery, for example after local anesthesia
12. Gastric/intestinal problems
13. Induction by physical agents or exercise
14. Use of drugs (ie, nonsteroidal antiinflammatory drugs, immunizations, hormones, laxatives, ear and eye drops, and alternative remedies)
15. Observed correlation to food
16. Relationship to the menstrual cycle
17. Smoking habits (especially use of perfumed tobacco products or cannabis)
18. Type of work
19. Hobbies
20. Stress
21. Quality of life related to urticaria and emotional impact
22. Previous therapy and response to therapy

*Data from European Academy of Allergy and Clinical Immunology/Global Allergy and Asthma European Network/European Dermatology Forum/World Allergy Organization 2013 urticaria guideline.[13]

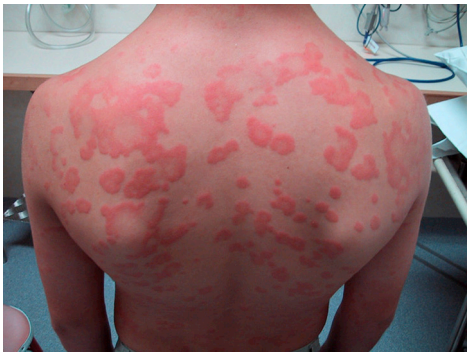

**Fig 1.** Acute urticaria. (Photograph courtesy of Pete Smith, MD, Griffith University, Brisbane, Queensland, Australia.)

**Table VI.** Diseases with urticarial lesions

| | |
|---|---|
| Syndromes presenting with wheals and/or angioedema | Cryopyrin-associated periodic syndromes, including familial cold autoinflammatory syndrome, Muckle–Wells syndrome, and neonatal-onset multisystem inflammatory disease/chronic infantile neurologic, cutaneous, and articular syndrome; Schnitzler syndrome; Gleich syndrome; and phospholipase Cg2–associated antibody deficiency |
| Diseases related to urticaria | Urticarial vasculitis; serum sickness–like reaction; bradykinin-mediated angioedema, including hereditary angioedema and angiotensin-converting enzyme–induced angioedema; mastocytosis; bullous pemphigoid; and arthropod bites |

A list of pertinent questions suggested by the European Academy of Allergy and Clinical Immunology/Global Allergy and Asthma European Network/European Dermatology Forum/World Allergy Organization guidelines[13] can be found in Table V.

Individual wheal lesions resolve within 24 hours, although the episode usually persists for several days, with new wheals occurring in different areas (Fig 1).

Angioedema is a sudden, pronounced, poorly defined swelling in deeper dermal, subcutaneous, or submucosal tissue. Lesions tend to be fainter in color, painful (particularly with delayed pressure angioedema), and last 48 to 72 hours. The lips, tongue, eyelids, genitalia, and rarely bowel are also affected. In some cases, angioedema can be associated with wheals, and these 2 can be difficult to separate, especially around the eyelids; in other cases, it may be mistaken for joint swelling. Isolated angioedema is clinically significant because some of these patients will have nonhistaminergic angioedema.[144]

For physical urticarias, the distribution pattern and morphology can give important clues for identifying potential triggers.[145] Patients with DPU

**Table VII.** Syndromes presenting with wheals or angioedema

| Syndrome | Mechanism | Clinical features |
|---|---|---|
| Cryopyrin-associated periodic syndromes[152] | *NLRP3* mutation and increased interleukin 1$\beta$ | Urticarial rash from birth, which is persistent and migratory. Systemic symptoms: fever, arthralgia, arthritis, malaise, and conjunctivitis. FCAS: short-term, for a few hours after cold exposure; MWS, longer episodes and unknown triggers; NOMID/CINCA: early onset. Association with bony overgrowth, mental retardation, optic nerve malformation, and chronic aseptic meningitis |
| Schnitzler syndrome[153] | N/A | Recurrent, asymptomatic/mildly pruritic wheals, recurrent fever, bone and joint pain, increased erythrocyte sedimentation rate, and monoclonal IgM gammopathy |
| Gleich syndrome[154,155] | N/A | Recurrent episodes of angioedema and eosinophilia; most associated with increased serum IgM |
| Phospholipase Cg2–associated antibody deficiency[156] | Phospholipase C$\gamma$2 (temperature-dependent intracellular signaling) | Life-long cold-induced urticarial; variable antibody deficiency, increased risk of infections, autoimmunity, and granulomatous disease |

*FACS*, Familial cold autoinflammatory syndrome; *IC*, intracellular; *IgM*, immunoglobulin M; *MWS*, Muckle–Wells syndrome; *NOMID/CINCA*, neonatal-onset multisystem inflammatory disease/chronic infantile neurologic, cutaneous, and articular syndrome.

usually complain of severe burning and pain, as well as systemic symptoms, such as arthralgias and malaise.[146] Lesions are induced when pressure from walking, tight clothes, sitting, or leaning is applied to sites like hands, feet, trunk, and buttocks.[147] For cold contact urticaria, the development of wheals occurs within minutes of cold contact. Extensive exposure (ie, swimming in cold water) can lead to systemic reactions, including shock.[148] Heat contact urticaria is rare[145]—wheals develop within a few minutes of exposure but resolve within a couple hours.[14] Solar urticaria appears on skin that is exposed to visible or ultraviolet light. When a large enough area is exposed, syncope, wheezing, and even anaphylaxis can be observed.[149]

The physical examination should also include any signs of residual purpura. When evaluating residual lesions, it is important to evaluate areas that are hard to reach by patients, because scratching can result in residual purpura or postinflammatory hyperpigmentation. If there is doubt, marking individual lesions and asking patients to monitor their duration can help differentiate between urticaria and urticarial vasculitis (UV). However, 50% of UV cases may present with lesions that are <24 hours old, making unresponsiveness to conventional antihistamines the main differentiating factor.[150]

In patients with isolated wheals associated with fever, joint/bone pain, or general malaise, autoinflammatory disease or UV should be considered as alternative diagnoses.[77,151] However, ≤16% of patients with CU report systemic symptoms associated with flares. The most frequent symptoms are asthenia, arthralgias, and abdominal pain, in ≤30% of cases. Headache, myalgias, retrosternal oppression, dyspnea, rhinorrhea, and ocular irritation are seen with less frequency.[1,110]

### Differential diagnosis

Urticaria can be part of several syndromes, and urticaria-like lesions can be found in various skin conditions; therefore, associated skin lesions and systemic signs and symptoms are crucial in achieving the correct diagnosis. Table VI lists urticarial diseases, Table VII summarizes the mechanism and clinical features of syndromes presenting with wheals or angioedema, and Table VIII shows the main dermatologic conditions that can present with urticaria-like lesions in addition to other clinical clues. An algorithm for the differential diagnosis of urticarial lesions is found in Table II.

## HISTOPATHOLOGY

### Key points

- **Histopathologic findings are usually mild, including sparse perivascular and interstitial mixed inflammatory infiltrate and upper dermal edema**
- **If vascular damage is present, UV needs to be considered**

Histopathologic findings can vary depending on chronicity, site (lesional vs uninvolved skin), and even subtype.[163] Although most cases are easy to

**Table VIII.** Diseases related to urticaria

| Disease | Clinical features | Histopathology |
|---|---|---|
| Urticarial vasculitis[157] | Urticarial lesions >24 h; residual purpura; more painful than pruritic angioedema in ≤40%; systemic symptoms: fever, arthralgia, arthritis, malaise, lymphadenopathy, and renal and liver involvement | Subtle findings; fibrinoid necrosis of vessel walls, karyorrhexis, extravasation of red blood cells, and endothelial swelling |
| Serum sickness–like reactions[158,159] | Urticarial lesions >24 h; fever, arthralgia, myalgia, arthritis, lymphadenopathy, glomerulonephritis, myocarditis, and neuritis; 1-2 weeks after antigen exposure (heterologous serum, or certain infections or drugs) | Leukocytoclastic vasculitis |
| Mastocytosis[160] | Urticarial lesions; reddish-brown macules and papules; positive Darier sign (urticarial reaction elicited by stroking lesion) | Uniformly spaced mast cells filling papillary dermis with or without reticular dermis; scattered eosinophils |
| Sweet syndrome (acute febrile neutrophilic dermatosis)[161] | Urticarial plaques >24 h; fever, leukocytosis; systemic symptoms: arthralgia, malaise, headache, and myalgia | Dense neutrophilic infiltrate in the papillary dermis; pronounced dermal edema |
| Bullous pemphigoid[162] | Elderly patients; multiple, erythematous, urticarial, pruritic, plaques with or without tense blisters | Subepidermal band of inflammatory infiltrate, with an abundance of eosinophils; perilesional DIF: linear complement 3 with or without immunoglobulin G at the BMZ |
| Insect bites | Long-standing urticarial lesions; central punctum | Variable; intraepidermal and papillary dermal edema; wedge-shaped perivascular and interstitial infiltrate: lymphocytes, eosinophils, and neutrophils |

*BMZ*, Basement membrane zone; *DIF*, direct immunofluorescence.

diagnose clinically, a biopsy specimen should be obtained if there is doubt. A universal feature across all urticarial biopsy specimens is the presence of a mixed cellular perivascular infiltrate surrounding the dermal postcapillary venules.[164] AU is associated with a more intense leukocytic infiltrate, an increased erythrocyte sedimentation rate, and leukocytosis.[129] Neutrophils are especially prominent in acute urticaria, in contrast to DPU, where the main infiltrate is composed of eosinophils in the reticular dermis.[165] Although distinctive pathological elements can be identified in different types of urticaria, the variability of these elements in individual lesions prevents their use as a sole diagnostic tool.

Angioedema shows similar findings; however, the reticular dermis and subcutaneous tissue are involved.[10]

Mast cells do not appear to be increased in number, although some reports have found up to a 10-fold increase in mast cell numbers in cases of CU.[163,166] There is controversy about the significance of the inflammatory infiltrate in urticarial lesions. Some authors have found an association between a predominantly eosinophilic inflammatory infiltrate and greater clinical severity scores,[166] while others found the same association with predominantly neutrophilic infiltrates.[167]

Vascular damage is not a finding of urticaria, and, if present, UV needs to be considered. UV affects the superficial vascular plexus and shows features of leukocytoclastic vasculitis, although the histologic findings tend to be subtle. Mild or focal fibrinoid changes are apparent only in few sections, and unlike classic leukocytoclastic vasculitis, neutrophils and karyorrhexis are mild. Immunofluorescence reveals vascular deposition of immunoglobulins and complement.[77] In patients with CU who are unresponsive to $H_1$ antihistamines, obtaining a skin biopsy specimen to assess for inflammatory infiltrates may therefore be warranted.

## WORK-UP

### Key points

- **In most cases of AU, extensive diagnostic work-up is not warranted**

- **For CU, a limited routine diagnostic work-up is recommended in a case-by-case basis**
- **A skin biopsy specimen may be helpful in cases of refractory urticaria or when alternative diagnoses are suspected**

### Acute urticaria

**Skin testing or immunoassays.** In general, no diagnostic work-up is necessary in the evaluation of AU. Further work-up may be warranted when allergic causes of AU are suspected. IgE-mediated reactions can be confirmed by skin-prick testing or chloramphenicol fluoroimmunoassay.

### Chronic urticaria

**Laboratory testing.** Extensive laboratory testing is not recommended in the evaluation of CU because it rarely identifies the cause or affects long-term management.[13,22,168] Both the European Academy of Allergy and Clinical Immunology/Global Allergy and Asthma European Network/European Dermatology Forum/World Allergy Organization international guidelines and the Joint Task Force on Practice Parameters recommend testing for underlying causes based on patient history (Table V) as well as specific tests to help elucidate the specific subtypes of CIndU (Table II).[13,22]

**Skin biopsy.** Obtaining a skin biopsy specimen is not recommended in patients with CU.[22] A skin biopsy should be considered in patients with refractory CU, when UV or other nonurticarial immunologic skin diseases are being considered, and in patients who are unresponsive to $H_1$ antihistamines to determine if there is a predominance of neutrophils.[22,169]

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