Urticaria

Pavel Kolkhir[1,2]✉, *Ana M. Giménez-Arnau*[3], *Kanokvalai Kulthanan*[4], *Jonny Peter*[5,6], *Martin Metz*[1,2] *and Marcus Maurer*[1,2]✉

Abstract | Urticaria is an inflammatory skin disorder that affects up to 20% of the world population at some point during their life. It presents with wheals, angioedema or both due to activation and degranulation of skin mast cells and the release of histamine and other mediators. Most cases of urticaria are acute urticaria, which lasts ≤6 weeks and can be associated with infections or intake of drugs or foods. Chronic urticaria (CU) is either spontaneous or inducible, lasts >6 weeks and persists for >1 year in most patients. CU greatly affects patient quality of life, and is linked to psychiatric comorbidities and high healthcare costs. In contrast to chronic spontaneous urticaria (CSU), chronic inducible urticaria (CIndU) has definite and subtype-specific triggers that induce signs and symptoms. The pathogenesis of CSU consists of several interlinked events involving autoantibodies, complement and coagulation. The diagnosis of urticaria is clinical, but several tests can be performed to exclude differential diagnoses and identify underlying causes in CSU or triggers in CIndU. Current urticaria treatment aims at complete response, with a stepwise approach using second-generation H1 antihistamines, omalizumab and cyclosporine. Novel treatment approaches centre on targeting mediators, signalling pathways and receptors of mast cells and other immune cells. Further research should focus on defining disease endotypes and their biomarkers, identifying new treatment targets and developing improved therapies.

Degranulation
The process by which cytoplasmic granules (originating from mast cells or other granulocytes) release their contents including preformed mediators such as histamine.

Wheals
Intermittent, circumscribed, superficial, central swellings, often surrounded by reflex erythema, that cause itching or burning sensations.

Angioedema
An intermittent, localized and self-limiting swelling of the subcutaneous or submucosal tissue, due to a temporary increase in vascular permeability, causing tingling, burning, tightness and, sometimes, pain.

✉*e-mail: pavel.kolkhir@charite.de; marcus.maurer@charite.de*

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Urticaria is a common and heterogeneous inflammatory skin disorder, with a lifetime prevalence of up to 20% worldwide[1,2]. The disease results from the activation and degranulation of skin mast cells, followed by the release of histamine and other mediators that lead to sensory nerve activation, vasodilatation, plasma extravasation and cellular recruitment[3,4]. This process causes the development of the disease-defining signs and symptoms, itchy wheals (hives) and angioedema or both (FIG. 1).

Urticaria is classified, first, based on its duration as acute urticaria (AU), lasting ≤6 weeks, or chronic urticaria (CU), lasting >6 weeks[4]. Urticaria is further divided into inducible and spontaneous forms. In inducible urticaria, the signs and symptoms are induced by a subtype-specific and definite trigger, for example cold in cold urticaria (ColdU). In spontaneous urticaria, the signs and symptoms appear unprompted, and there are no definite triggers, although stress, infections and other aggravators can increase disease activity in some patients. Spontaneous urticaria is more common than inducible urticaria and both can coexist in the same patient[4–6] (TABLES 1 and 2).

Most cases of AU resolve within 1 week, and <40% of cases become chronic (see Supplementary Table 1). CU often lasts for several years before spontaneous remission occurs (see Supplementary Tables 2 and 3). AU is mostly spontaneous and of unknown cause, although infections and the intake of drugs or foods are thought to be relevant in some patients (see Supplementary Table 4). The underlying causes of chronic inducible urticaria (CIndU) remain unknown, whereas two causes of chronic spontaneous urticaria (CSU) (previously known as chronic idiopathic urticaria) are recognized: autoallergy (also called type I autoimmunity) with IgE autoantibody involvement, and type IIb autoimmunity with IgG autoantibody involvement[7,8]. These mast cell-activating autoantibodies along with cell infiltration, coagulation and complement activation are thought to be key drivers of the pathogenesis of CSU[9,10].

The burden of CU for patients and society is substantial. CU manifestations have a strong effect on health-related quality of life, including sleep impairment, diminished physical and emotional well-being and poor performance at school and work[11,12]. Current treatment options are still limited and are not effective in around one-third of patients with CU. Novel targeted treatments are needed, and several promising drugs are already under development[13].

In this Primer, we discuss the current knowledge of urticaria epidemiology, diagnosis, screening, management and quality of life, and highlight recent advances in the understanding of disease pathogenesis and targeted treatment. Other pathophysiologically and clinically distinct conditions that present with wheals and/or

Author addresses

[1]Urticaria Center of Reference and Excellence (UCARE), Institute of Allergology, Charité — Universitätsmedizin Berlin, Berlin, Germany.
[2]Allergology and Immunology, Fraunhofer Institute for Translational Medicine and Pharmacology ITMP, Berlin, Germany.
[3]Urticaria Center of Reference and Excellence (UCARE), Department of Dermatology, Hospital del Mar, Institut Mar d'Investigacions Mediques, Universitat Autònoma, Barcelona, Spain.
[4]Urticaria Center of Reference and Excellence (UCARE), Department of Dermatology, Faculty of Medicine Siriraj Hospital, Mahidol University, Bangkok, Thailand.
[5]Urticaria Center of Reference and Excellence (UCARE), Division of Allergy and Clinical Immunology, Department of Medicine, University of Cape Town, Cape Town, South Africa.
[6]Urticaria Center of Reference and Excellence (UCARE), Allergy and Immunology Unit, University of Cape Town, Lung Institute, Cape Town, South Africa.

angioedema, for example urticarial vasculitis, autoinflammatory syndromes and bradykinin-mediated angioedema, are briefly discussed as differential diagnoses. Detailed tables of study findings relating to epidemiology and diagnosis, with accompanying references, can be found in the Supplementary information.

Epidemiology

Prevalence and incidence

For 2017, the prevalence of urticaria was estimated at 86 million cases and the annual incidence at 160 million cases globally[14]. However, each urticaria subtype has its own prevalence within different populations. The prevalence of AU is highest in children <5 years of age[14–16], whereas CU, especially CSU, is most prevalent in women >30 years old[6,17–21]. Adult patients with CSU are older than adult patients with CIndU (average age ~30–70 years versus ~20–40 years) and have older age of disease onset (~30–50 years versus ~20–35 years). In adults, all types of urticaria are more prevalent in women than in men, except for cholinergic urticaria (CholU), which is more prominent in both male adults and children; female predominance is absent or is less prominent in younger children[21] (TABLE 1; see Supplementary Tables 2 and 3).

All ethnicities are affected; however, the prevalence of AU and CU was higher in non-white patients in some studies[15,19,22] but not all[23]. The lifetime prevalence of all types of urticaria and AU is 3–22% and 6–19%, respectively (see Supplementary Table 5). The overall lifetime prevalence of CU is 4.4%[22], and the point prevalence of CU (1-year prevalence in most studies) ranges from ≤1.5% in the USA and Europe to 3–4% in Mexico, Korea and China (FIG. 2; see Supplementary Table 5).

No significant changes in the global prevalence, incidence and the years of life lived with disability were seen for urticaria between 1990 and 2017 (REF.[14]). The consistent increase in CU prevalence in South Korea[21,24], Italy[25,26] and Taiwan[27] may be linked to country-specific demographic, environmental and behavioural factors and changes.

CIndU is less prevalent than CSU[6,28]. The pooled rate of all CIndU subtypes was 13%[29] and that of CSU was ~60–90% across all cases of CU (see Supplementary Table 6). The most prevalent types of CIndU are symptomatic dermographism, CholU and ColdU, in both adults and children[21,30], whereas aquagenic urticaria, solar urticaria, heat urticaria, vibratory angioedema and contact urticaria are rare, that is, are seen in <2–3% of all CU cases (TABLE 2; see Supplementary Table 6). Delayed pressure urticaria is rarely seen as an isolated disorder but present in combination with CSU in up to 36% of patients with CU (TABLE 2; see Supplementary Table 6).

Natural course

The average duration of AU is ≤1 week. The rates of progression of AU to CU are between 5% and 39% in most studies (see Supplementary Table 1). CSU is of shorter duration than CIndU, with a mean or median disease duration of ~1–4 years in most studies (see Supplementary Table 2), and the cumulative weighted average estimates for spontaneous remission at 1, 5 and 20 years are 17%, 45% and 73%, respectively[31]. CSU relapses in 6–31% of patients (see Supplementary Table 2). The mean or median duration of CIndU and its three most common subtypes (symptomatic dermographism, CholU and ColdU) was 2–12 years, 2–5 years, 3–8 years and 2–9 years, respectively. Remission of CIndU within 5 years occurs in only around one-third of patients, with the highest rates in symptomatic dermographism and the lowest in CholU and ColdU[30] (see Supplementary Table 3). Various factors and markers have been found to be associated with urticaria natural course, phenotypes, endotypes, clinical and laboratory characteristics and response to treatment (see Supplementary Box 1).

Risk factors

Risk factors reported for AU include high population density[15] and personal[32] and parental history of allergic diseases[2,33]. Higher prevalence and/or higher risk of having AU may be associated with poverty and lower socio-economic status[14,15], whereas risk for CU was linked to high income and socio-economic status in some studies[2,23,34] but not all[35,36]. In studies involving twins, genetic factors could partly explain susceptibility to urticaria[32]. The role of polymorphisms of several genes, including *TNFRS11A, TBXA2R* and *PLA2G4A*[37], has been suggested in susceptibility to AU and/or angioedema induced by multiple NSAIDs.

Genetic predisposition to CU has been associated with gene polymorphisms of IFNγ, IL-6, IL-17RA, IL-10, TGFβ, IL-6, tumour necrosis factor (TNF), PTPN22, IL-1, IL-2 and HLA class I and II alleles[38]. Some of these genes, such as *PTPN22*, and HLA alleles, for example HLA-DR4 allele, are also responsible for susceptibility to various autoimmune disorders. For example, HLA-DR4 was strongly associated with autoimmune CSU defined by a positive basophil histamine release assay (BHRA)[39] and other autoimmune diseases, for example rheumatoid arthritis and type 1 diabetes mellitus. CSU, especially in middle-aged women with autoimmune CSU[40], is associated with an increased risk of developing autoimmune disease within 10 years after the diagnosis of CSU[41]. For example, women with CSU were 23 and 20 times more likely to also have hypothyroidism and rheumatoid arthritis, respectively, compared with the control group[41]. Diagnosis of CSU was made in ~80% and ~20% of patients before and after diagnosis of autoimmune

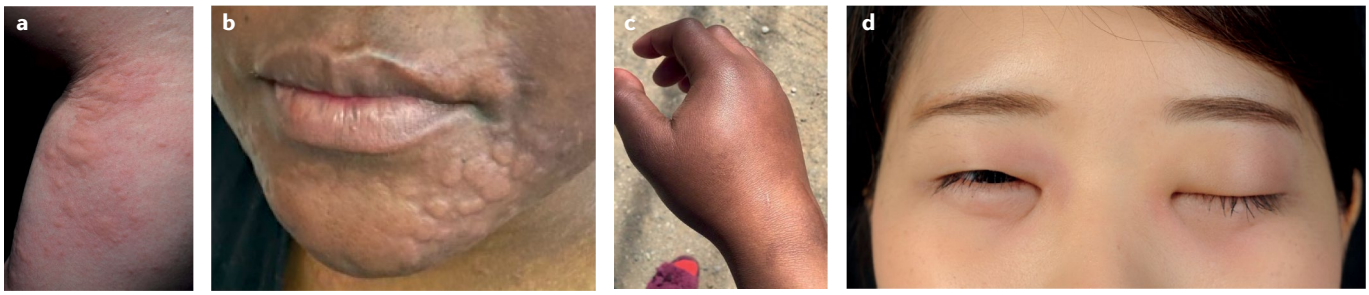


Fig. 1 | **Typical presentation of urticaria. a**,**b** | Wheals. **c**,**d** | Angioedema.

diseases, respectively, including rheumatoid arthritis, systemic lupus erythematosus, type I diabetes mellitus and coeliac disease[41]. Patients with autoimmune thyroid diseases, especially female patients, had a considerably higher risk of CSU development[42]. Up to 25% of patients with CSU, especially those with positive markers of autoimmune urticaria[43–45], had a family history of CSU (see Supplementary Table 7). In addition, female patients with peptic ulcer disease[46] and abnormal uterine bleeding[47] have been shown to have a higher CU risk.

Geographical differences in frequency of CholU and ColdU were reported suggesting that some environmental factors, for example temperature and altitude, might increase the risk of developing CIndU[48].

Healthcare use and annual treatment costs

Urticaria, especially CU, is associated with considerable healthcare utilization and economic burden, including both regular and unanticipated healthcare visits, costs due to laboratory expenses and indirect costs due to the absence from work or reduced efficiency[11,49]. Patients with CU, especially those with angioedema, more frequently visit physicians, mostly family doctors, allergists and dermatologists, and emergency rooms, and are more frequently hospitalized than individuals without urticaria[12,49,50]. Patients with CIndU were more often hospitalized than patients with CSU (paediatric, 15.5% versus 9.9%; adult, 7.8% versus 4.6%; respectively)[6]. Average annual economic costs for a patient with CSU ranged from PPP$907 (purchasing power parity dollars) in Italy to PPP$2,984 in France, mostly due to therapies and inpatient visits[12].

Mechanisms/pathophysiology

Skin mast cells have a central role in urticaria pathogenesis and are found in the upper papillary dermis as well as the deep dermis and subcutis, mostly around cutaneous blood vessels and sensory nerves. Their activation with subsequent degranulation drives the development of itchy wheals and/or angioedema[3].

Acute urticaria

The pathogenesis of AU is poorly investigated. Acute spontaneous urticaria, as well as wheals and/or angioedema in patients with anaphylaxis, have been described to result from type I hypersensitivity reactions to foods, drugs and other allergens[51]. Type I hypersensitivity, also known as an immediate IgE-mediated reaction, describes interaction between exoallergen and a pre-existing complex of an IgE antibody bound to its high-affinity receptor, FcεRI, on mast cells and basophils that leads to cell activation and degranulation[52]. NSAID-induced urticaria and/or angioedema is IgE-mediated or T cell-mediated, or due to the pharmacological inhibition of cyclooxygenase 1 (COX1) and increased levels of cysteinyl leukotrienes[53]. Acute contact urticaria can develop in response to direct contact with allergens with previous sensitization[54] and urticariogenic substances without prior sensitization, for example after touching stinging nettles[4].

Chronic spontaneous urticaria

Mast cells. The development of wheals and angioedema in CSU is dependent on mast cell-activating signals and receptors, signalling pathways, inhibitory receptors and mediators, which are targets of current and future therapy[3,10,13] (FIG. 3). Mast cells express many activating receptors including FcεRI, MRGPRX2, C5aR, PAR1, PAR2, chemoattractant receptor-homologous molecule expressed on T helper 2 cells (T_H2 cells) (CRTh2) and cytokine receptors, which can be activated by various signals[13]. Interaction of stem cell factor (SCF), produced by fibroblasts, endothelial cells and mast cells, with its receptor KIT (CD117) on mast cells is a major driver of mast cell differentiation, migration, proliferation, survival and apoptosis[55]. Activation of FcεRI involves several cytoplasmic signalling proteins, for example. LYN, spleen tyrosine kinase (SYK) and Bruton's tyrosine kinase (BTK), which phosphorylate downstream signalling targets and induce mast cell activation and degranulation[56] The first step in FcεRI-mediated signalling is the phosphorylation of the FcεRI β-chain and γ-chain by LYN followed by activation of SYK and BTK. The cytosolic tyrosine kinase BTK is the central positive regulator of FcεRI-mediated mast activation and cytokine production[56,57]. In addition to its role in mast cell activation, BTK is also required for B cell receptor (BCR) signalling[56,57]. In addition to activating receptors, mast cells express a few inhibitory receptors, such as sialic acid-binding immunoglobulin-like lectin 8 (Siglec 8), CD200R, CD300a and FcγRIIb[58], which can silence mast cells and block mast cell activation upon interaction with their ligands.

CSU symptoms occur mainly due to the release of histamine, but also by a broad range of other produced and secreted mediators, including tryptase, prostaglandin D2 (PGD_2), TNF, IL-4, IL-5, IL-13, IL-17 and IL-31, which can exert effects on resident skin cells and other

Mast cells
Immune cells of the myeloid lineage that contain many granules rich in histamine and other mediators and are present in connective tissues throughout the body, especially skin, near blood vessels, lungs and intestines.

Cysteinyl leukotrienes
A family of inflammatory lipid mediators synthesized from arachidonic acid by various cells including mast cells, eosinophils and basophils.

Table 1 | **Comparison of different types of urticaria**

Parameter	Acute urticaria	Chronic spontaneous urticaria	Chronic inducible urticaria
Duration (weeks)[4]	≤6	>6	>6
Point prevalence (%)[a]	≤14	0.02–2.7	0.05–1.5
Remission rates at 1 year (%)[a]	~60–90	10–80[b]	0–49
Sex predominance[144 a]	Female	Female	Female; male in CholU
Typical age of onset[a]	Any age, likely more frequent in children <5 years old	6–9 years old (children); 30–50 years old (adults)	4–12 years old (children); 20–35 years old (adults); CholU, 10–30 years old; DPU, ~40 years old
Aetiology[4 a]	Idiopathic, infections, drugs, food, insect stings, inhalant allergens, physical factors	Idiopathic, autoimmune; rarely infections, cancer, hypothyroidism, hyperthyroidism, rheumatic diseases, type I hypersensitivity	Subtype-specific triggers including cold, heat, pressure, ultraviolet and visible light, vibration, water, sweating, contact allergens
Risk factors	High population density, allergic diseases in personal and parental history[2,15,32]	Autoimmune thyroid diseases[42]	Unknown; possibly environmental factors, for example temperature or climate[48]
Triggers[4]	Differ	Non-definite, non-specific, for example stress, NSAIDs or foods	Definite, specific[c]
Proposed pathogenesis[4,9,10,53,106]	Unknown, allergic reactions, COX1 inhibition	Autoimmunity, cell infiltration, activation of coagulation and complement systems	Differs based on a subtype; immunological or non-immunological
Symptom frequency[4]	Usually, daily or after exposure to causative factor, for example allergen	Daily or almost daily or an intermittent–recurrent course	When trigger is present
Frequent comorbidity[5]	Infection	CIndU, autoimmune diseases, especially thyroiditis, mental health disorders	CSU, probably allergic diseases
Basic screening tests[4]	None	Differential blood count and ESR and/or CRP; IgG anti-TPO and IgE in specialist care	Provocation testing

CholU, cholinergic urticaria; CIndU, chronic inducible urticaria; COX1, cyclooxygenase 1; CRP, C-reactive protein; CSU, chronic spontaneous urticaria; CU, chronic urticaria; DPU, delayed pressure urticaria; ESR, erythrocyte sedimentation rate; TPO, thyroid peroxidase. [a]Based on data from Supplementary Tables 1–6. [b]Cumulative weighted average estimate for the proportion of patients remitting at 1 year was 17%[31]. [c]Rare subtypes of inducible urticaria exist in which the combined presence of two or more definite and specific triggers is required for the induction of wheals, angioedema or both, for example cold-induced CholU. Two or more types of CIndU with and without CSU are seen in about 1% and 2–3% of patients with CU, respectively[254].

recruited target cells, for example T cells, eosinophils and basophils[3,13].

Cell infiltrate. In CSU, perivascular and interstitial inflammatory cellular infiltrates, resembling an allergic late-phase reaction, include eosinophils, neutrophils, lymphocytes and basophils[9,59–61]. Infiltrating cells are thought to migrate from the blood into the skin in response to chemotactic factors, for example eotaxins, MCP3, RANTES, IL-5, C3a, C5a, TNF, IL-17 and platelet-activating factor (PAF), released by mast cells, activated endothelial cells, T_H2 cells, dermal fibroblasts and other cells[9]. Cell adhesion molecules, for example P-selectin, E-selectin, ICAM, VCAM and PECAM, are upregulated on the surface of endothelial cells in the lesional skin of patients with CSU due to action of histamine, thrombin, TNF and other factors[9].

Blood basopenia and eosinopenia that are observed in ~10–15% of patients with CSU may reflect the transport of cells into the skin, and are associated with CSU activity, presence of autoantibodies and poor response to H1 antihistamines (H1-AH) and omalizumab[62,63]. Perivascular eosinophils and neutrophils appeared in wheals 30 min after intradermal injection of autologous serum and, along with T lymphocytes, increased in numbers over the following 2 h with a decrease by 48 h (neutrophils) or later (eosinophils and lymphocytes)[64]. Blood and skin-migrated basophils can contribute to the CSU pathogenesis by releasing histamine, leukotrienes and cytokines via activation of FcεRI and C5aR[65,66]. Eosinophil granule proteins such as major basic protein (MBP) were detected in the wheals of patients with CSU[67,68]. MBP was able to induce mast cell activation and degranulation, representing a putative mechanism of crosstalk between eosinophils and mast cells in CSU[67]. Activation of eosinophils can occur due to mast cell mediators, namely IL-5, TNF, PAF and eotaxin, and also IgG autoantibodies to the low-affinity IgE receptor[69]. Activated eosinophils can also release SCF, a growth factor for mast cells. Finally, eosinophils might be key players in activation of the coagulation cascade and of Mas-related G-protein-coupled receptor X2 (MRGPRX2) on mast cells via expression of tissue factor and release of MRGPRX2 agonists, respectively[67,69].

T_H2 cells are a predominant type of lymphocyte in CSU skin biopsy samples but T_H1 cells and T_H17 cells are also present[9]. T_H2 cells are highly involved in allergic diseases, releasing a broad range of cytokines, stimulating IgE production and mast cell, basophil and eosinophil activation. In patients with CSU, cytokine levels and/or expression were increased in the blood and/or lesional skin, for example IFNγ, TNF, TGFβ, IL-1β, IL-3, IL-4,

Eotaxins
A CC chemokine subfamily of potent eosinophil chemoattractants including CCL11 (eotaxin 1), CCL24 (eotaxin 2) and CCL26 (eotaxin 3).

Autologous serum skin test (ASST). Intradermal injection of autologous serum to assess autoreactivity associated with autoantibodies and other histamine-releasing factors; defined as a serum-induced wheal response with a diameter ≥1.5 mm compared with that of the saline-induced response.

Tissue factor
The high-affinity receptor expressed on eosinophils, epithelial cells and other cell types, and cofactor for factor VII (FVII)/FVIIa important for initiation of blood coagulation.

IL-5, IL-6, IL-13, IL-17, IL-23, IL-24, IL-31 and IL-33, and correlated with disease activity, for example TNF, IL-6, IL-17, IL-23 and IL-24, and autologous serum skin test (ASST) positivity, for example IL-17 (REF.[9]).

Coagulation cascade and complement. Eosinophils and dermal microvascular endothelial cells can express a large amount of tissue factor on their surface in response to tissue factor inducers, for example histamine, vascular endothelial growth factor (VEGF), LPS, TNF, IL-6, IL-33 and IL-1β[70]. Tissue factor can activate the extrinsic coagulation cascade leading to the production of activated coagulation factors, such as factor Xa (FXa) and FIIa (thrombin)[71,72].

Coagulation factors, histamine, VEGF[73], bradykinin, PAF and/or other molecules can lead to gap formation between vascular endothelial cells via protease-activated receptor 1 (PAR1), other specific receptors and/or a direct action on endothelial cells[9]. This results in the leakage of plasma that can contain autoantibodies to IgE or FcεRI, and/or autoantigens for specific IgE bound to mast cells in the skin with subsequent activation of mast cells and wheal and flare formation[9]. In addition, thrombin and FXa may induce mast cell degranulation via action on PAR1 and PAR2, respectively[10,74]. Furthermore, complement component C5a is thought to be produced following the activation of extrinsic coagulation, fibrinolysis and/or binding of IgG anti-FcεRI to FcεRI on mast cells and basophils[10]. Activated coagulation factors (FXa and FIIa) and plasmin can produce C5a and C5b from C5, and/or C3a and C3b from C3. C3a and C5a in leaked plasma can activate mast cells and basophils via C3aR and C5aR, respectively[10,75]. Finally, functional specific IgE antibodies to tissue factor were reported to release leukotriene C4 by tissue factor-stimulated peripheral basophils[76].

Table 2 | **Classification of chronic inducible urticaria**[4,106]

CIndU type		Prevalence of CIndU (%)			Trigger	Time to symptoms after exposure	Clinical presentation	Example of provocation test devices
		General population	Patients with CU					
			CIndU only	CIndU with CSU				
Physical	Symptomatic dermographism	0.12	3–27	0–35	Scratching or rubbing of the skin	5–10 min	Linear wheals due to shear force acting on the skin	FricTest, dermographic tester
	ColdU	~0.019	1–9[a]	0–2	Cooling and rewarming of the skin; exposing to cold air, liquids or solid objects	5–10 min	Wheals, anaphylaxis in severe cases	TempTest, melting ice cube in the plastic bag
	Delayed pressure urticaria	No data available	0–3	0.3–36	Sustained pressure stimulus	6–8 h	Angioedema, erythema	Weighted rods, dermographic tester, suspension of weights over shoulder
	Solar urticaria	0.0031	0.3–3	0.2	Sunlight	5–10 min	Wheals	UVA and UVB irradiation
	Heat urticaria	No data available	0.4–0.5	Very rare	Heating of the skin	5–10 min	Wheals	Heat source, TempTest
	Vibratory angioedema	No data available	Very rare	Very rare	Vibration	5–10 min	Angioedema	Vortex vibrator
Other	CholU	0.023 (lifetime 0.1)	1–7	0–7	Active, for example exercise, and passive warming, for example hot bath	5–10 min	Itchy tiny wheals with a pronounced flare reaction; anaphylaxis in severe cases	Exercise machine, hot bath
	Contact urticaria	Variable, depending on trigger	1.5	No data available	Various substances	Minutes to days	Wheals spreading beyond the area of contact (immunologic) or not (non-immunologic)	Open controlled application testing, skin prick testing, patch testing, specific IgE
	Aquagenic urticaria	No data available	0.1–1	Very rare	Water	5–10 min	Wheals	Compress or towel soaked with 35–37 °C water

Based on data from Supplementary Tables 5, 6 and 9. Point prevalence of CIndU is presented for the general population. CholU, cholinergic urticaria; CIndU, chronic inducible urticaria; ColdU, cold urticaria; CSU, chronic spontaneous urticaria; CU, chronic urticaria. [a]The pooled prevalence of ColdU among patients with CU and CIndU was 7.6% and 26.1%, respectively[255].

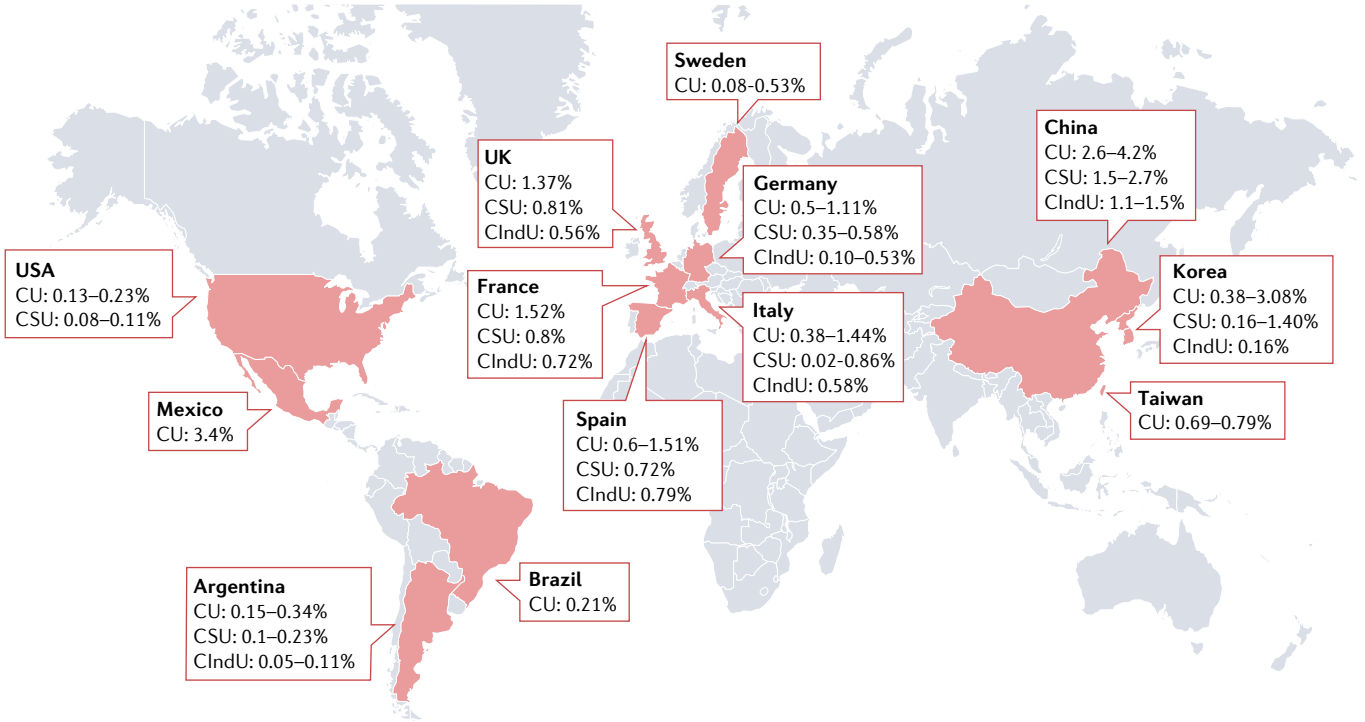


Fig. 2 | **Global prevalence of chronic urticaria.** A point prevalence of chronic urticaria (CU) in children, adults and/or both is presented where available. The lowest prevalence rates were observed in the USA and Europe, whereas the highest rates were reported in Mexico, China and Korea. Detailed information can be found in Supplementary Table 5. CIndU, chronic inducible urticaria; CSU, chronic spontaneous urticaria.

Activation of coagulation and fibrinolysis in patients with CSU is reflected in increased mean platelet volume, levels of D-dimer, fibrin and fibrinogen degradation products, prothrombin fragment 1 + 2, FVIIa and other molecules[41,71]. An increase in blood markers of thrombin generation and fibrinolysis, for example D-dimer, was linked to severe CSU and a decrease was observed during CSU remission[77]. Although activation of the coagulation cascade happens in CSU, it is considered mostly a local process with active fibrinolysis without increased risk for thrombotic events[71].

In patients with CSU, increased C-reactive protein (CRP) levels correlated with increased D-dimer, IL-6, C3 and C4 levels as well as CSU activity and ASST positivity[78,79]. This finding supports a close link between autoimmunity, inflammation, complement and coagulation activation pathways in CSU pathogenesis that may lead to maintenance and amplification of urticarial inflammation.

Autoantibodies. Antibodies of IgE, IgA, IgM and IgG classes are thought to be critically involved in the pathogenesis of CSU[80–82]. IgE binds to the α-subunit of its high-affinity receptor, FcεRI, on mast cells and basophils and, if present at high concentrations, can activate these cells regardless of the specific antigen[83]. In addition, the cross-linking of IgE by their respective allergens, autoallergens and IgG anti-IgE antibodies can lead to mast cell and basophil activation and mediator release in allergic, autoallergic and autoimmune urticaria, respectively[8,82,84,85].

Clinically relevant allergy as a cause of CSU is rare[84,86]. IgE antibodies to autoantigens, for example thyroid peroxidase (TPO), eosinophil peroxidase (EPO), double-stranded DNA, tissue factor, ECP, FcεRI, thyroglobulin and IL-24, are found in up to two-thirds of patients with CSU and some of these antibodies, for example IgE anti-IL-24 and IgE anti-TPO, were shown to activate mast cells and/or basophils in vitro[8,87]. Furthermore, evidence in support of IgE autoantibodies as a driver of CSU includes high rates of positive skin prick tests with TPO in patients with CSU with increased levels of IgE anti-TPO and successful experiments of passive transfer of IgE anti-TPO[88]. Cross-reactivity between proteins, for example between TPO (not present in the skin) and EPO (present in the skin)[89], and expression of autoallergens in the skin, for example IL-24, might explain why IgE–autoallergen interaction leads to activation of mast cells in skin rather than in other organs[90].

IgG autoantibodies to IgE and FcεRI were the first autoantibodies described in the context of autoimmune CSU. Most studies report that 20–50% of patients with CSU have these autoantibodies[91]. Since 2013, when a taskforce position paper was published, autoimmune CSU associated with these autoantibodies is defined by triple positivity for presence of IgG autoantibodies by immunoassay, functionality of autoantibodies assessed by basophil tests (basophil activation test and/or BHRA) and skin autoreactivity assessed by ASST[92]. If these strict criteria are applied, only 8% of patients with CSU are diagnosed with autoimmune CSU[7].

It is still a matter of debate whether clearly defined and distinct auto-IgE and auto-IgG endotypes exist. Although real overlap rates are still unknown, there is growing evidence of co-expression of IgG autoantibodies and other types of autoantibodies, specifically IgE, IgM and IgA autoantibodies, in the same patient[80,81]. IgE autoantibodies might appear in blood first, followed by other types of autoantibodies over the course of the disease.

Neurogenic inflammation. In CSU, the bidirectional interaction of mast cells, other immune cells and sensory nerves is thought to exist through release of histamine, IL-31, neuropeptides and other mediators[67,93,94]. This vicious cycle causes vasodilatation, plasma extravasation, neurogenic inflammation, pruritus and other urticaria symptoms, and might be supported via MRGPRX2-mediated activation of mast cells[95]. MRGPRX2 is a receptor for a broad range of exogenous and endogenous substances and is responsible for IgE-independent activation of mast cells[96]. MBP and EPO induced histamine release from human skin mast cells via MRGPRX2 (REF.[67]). Levels of substance P, a neuropeptide and MRGPRX2 agonist, were elevated in CSU, correlated with disease activity in some studies[97], and provocation with MRGPRX2 agonists revealed an increased skin reactivity in patients with CSU[98]. Lastly, the number of MRGPRX2-expressing mast cells has been found to be increased in patients with CSU[67].

Chronic inducible urticaria

The pathogenesis of CIndU is largely unknown. Autoallergic IgE-mediated mast cell activation was suggested in symptomatic dermographism, ColdU, solar urticaria and CholU by passive transfer experiments and/or the efficacy of omalizumab[99]. IgE autoantibodies might be produced to a skin-derived protein released upon stimulation, for example by cold[100]. In solar urticaria, molecular alteration of chromophores by solar electromagnetic radiation and their binding to surface-bound IgE on mast cells, leading to their activation, have been suggested[101]. In CholU, blockade of the sweat gland duct might lead to sweat reflux and leakage into the dermis inducing the symptoms of CholU due to production of a sweat antigen. Specific IgE to sweat antigen MGL_1304 have been identified in sera of some patients with CholU[102]. Another proposed mechanism in CholU is reduced expression of cholinergic receptor M3 (CHRM3) in eccrine sweat gland epithelial cells, which leads to escape of acetylcholine with acetylcholine-mediated degranulation of adjacent mast cells[102]. IgG and/or IgM directed to IgE were shown in ColdU[100]. In patients with heat urticaria, few cases of a positive reaction on intradermal testing with heated autologous serum, presumably containing denatured IgE and inactivated complement, were described[103]. Hereditary vibratory angioedema can present as an autosomal dominant variant due to a gain-of-function mutation in adhesion G-protein-coupled receptor E2 (ADGRE2), located on mast cells, which might decrease inhibitory interaction between the α-subunit and the β-subunit of this receptor leading to sensitization of mast cells to vibration-induced degranulation[104]. Delayed pressure urticaria is thought to occur via a non-immunologic mechanism with involvement of many pro-inflammatory mediators other than histamine, for example IL-1, IL-6, IL-3 and TNF[105]. In contrast to other CIndU, delayed pressure urticaria showed a substantial leukocyte infiltration in the dermis perhaps due to a sustained initiating stimulus[105]. Contact urticaria can be classified as an immunological reaction, that is IgE-mediated or T cell-mediated, or a non-immunological reaction[106]. Hypotheses explaining pathogenesis of aquagenic urticaria include the synthesis of a mast cell-degranulating substance due to interaction between water and a component in or on the skin or sebum; changes in osmotic pressure surrounding hair follicles and increased passive diffusion of water; the existence of water-soluble antigens in the epidermis; and a histamine-independent mechanism[107].

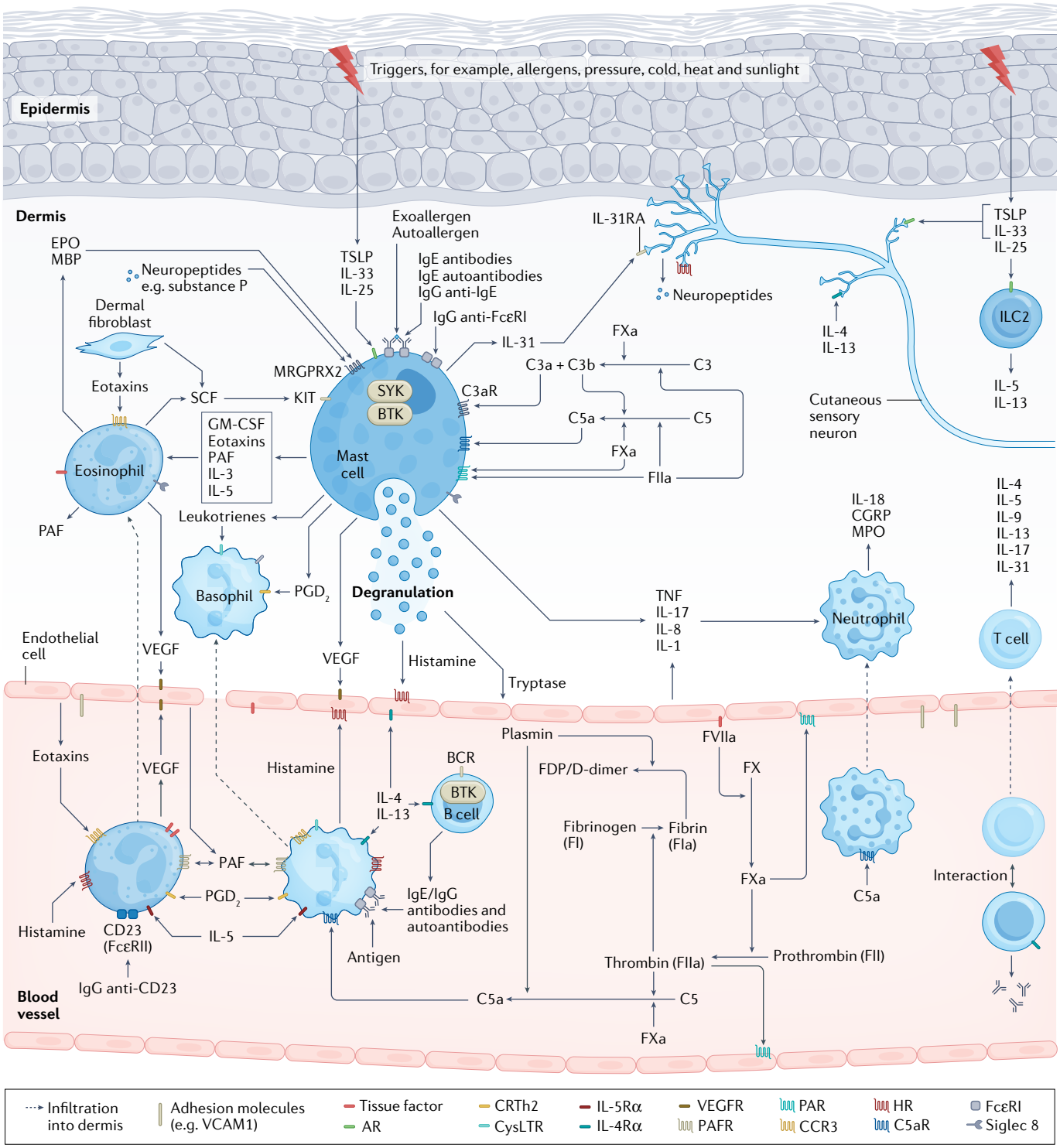
Diagnosis, screening and prevention

Diagnosis

The clinical presentation of urticaria is very similar in all age groups, ethnicities and genders. Wheals and angioedema occur with the same anatomical distributions across all skin tones. However, erythema related to whealing is more difficult to detect in pigmented skin[108]. A detailed history and physical examination are the essential first steps in the diagnostic workup of all patients with urticaria. However, as wheals and angioedema are transient and may not be present at physical examination, physicians should also review patients' pictures or their documentation of signs and symptoms (FIG. 4). Diagnosis of urticaria is usually straightforward irrespective of its type or subtype[4] (see Supplementary Fig. 1).

Acute urticaria. By definition, AU is self-limiting and does not require routine or extensive diagnostic tests unless strongly suggested by patient history[4]. For example, in patients with a history of type I food allergy or drug hypersensitivity, urticaria symptoms can appear immediately after a contact with respective allergens and allergy tests may help avoid re-exposure to relevant causative factors.

Chronic spontaneous urticaria. Most patients with CSU present with only wheals (~57%), whereas the occurrence of wheals and angioedema (~37%) or only angioedema (~6%) is less common (see Supplementary Table 8). The signs and symptoms of CSU can occur spontaneously at any time of the day but commonly during the evening and night[109], which may reflect circadian variations in mast cell activation[110] and differences in the underlying pathogenesis. For example, the presence of nocturnal symptoms has been associated with an autoimmune endotype of CSU[111]. Wheals can occur anywhere, but favour the arms and legs[109]. Angioedema appears most commonly on the face, for example lips and eyelids, but also on hands and feet and other body parts[1]. In most patients with moderate or severe CSU, wheals and/or angioedema occur on a daily or nearly daily basis or show an intermittent–recurrent course[4].



Oral drug provocation testing
The gold standard for diagnosis of NSAID-mediated reactions including identification of a culprit drug, confirming or excluding cross-reactivity, and finding the most likely tolerated alternative drug.

In some patients with CSU, stress, foods, drugs (mostly NSAIDs) or infections can lead to exacerbation. NSAID hypersensitivity is observed in up to 30% of patients with CSU and is classified as NSAID-exacerbated cutaneous disease[53]. CSU exacerbation occurs within minutes or hours after the intake of COX1 inhibitors (selective COX2 inhibitors are usually tolerated)[112] and can be confirmed by oral drug provocation testing[53].

The current international urticaria guideline has introduced the 7C concept, that is, seven aims of the diagnostic workup in patients with CSU[4]. The 7C concept includes ruling out differential diagnoses (confirm); looking for markers of autoimmune urticaria (cause); identifying potential triggers (cofactors); checking for autoimmunity, mental health disorders and other comorbidities; identifying problems with sleep, distress, sexual health and social performance (consequences); assessing potential biomarkers or predictors of treatment response (components); and monitoring CSU activity, impact and control (course).

◀ Fig. 3 | **Key pathways of urticaria pathogenesis including current and future therapeutic targets.** Activation and degranulation of mast cells leads to the development of signs and symptoms of urticaria due to the release of histamine and other mediators, which activate sensory skin nerves (itch), dilate skin blood vessels (erythema) and induce plasma extravasation (oedema and influx of other immune cells). In allergic urticaria, release of alarmins, TSLP, IL-33 and IL-25, by the epithelium, activation of skin-resident group 2 innate lymphoid cells (ILC2), polarization of T cells (mostly T helper 2 cells (T_H2 cells)) with release of T_H2 cytokines, for example IL-4, IL-5 and IL-13, and allergen-specific IgE production by B cells enable subsequent cross-linking of IgE–FcεRI complexes on the surface of mast cells by allergens, which triggers mast cell activation. Chronic spontaneous urticaria (CSU) can appear due to a chain of complex multistep interlinked events including cell infiltration (mostly eosinophils, basophils, neutrophils and T cells), autoimmunity (for example, IgE/IgG histamine-releasing autoantibodies), neurogenic inflammation (via histamine-dependent and histamine-independent itch signalling pathways mediated by cutaneous pruriceptive sensory nerves), activation of the complement cascade (for example, via production of anaphylatoxin C5a) and activation of tissue factor-initiated extrinsic pathway of the coagulation cascade. Here, receptors (for example, FcεRI, C5aR, MRGPRX2, Siglec 8, KIT and IL-4Rα), signalling pathways (for example, BTK and SYK) and mediators (for example, histamine, tryptase, IL-5, IL-17 and IL-31) of mast cells, eosinophils, basophils and/or other immune cells involved in urticaria, as well as activating signals (for example, IgE anti-autoallergens), are the targets for current therapy and drugs in development. In chronic inducible urticaria (CIndU), similar mechanisms of mast cell activation including autoallergy and/or autoimmunity may have a role. AR, alarmin receptors; BCR, B cell receptor; BTK, Bruton's tyrosine kinase; CGRP, calcitonin gene-related peptide; CRTh2, chemoattractant receptor-homologous molecule expressed on T_H2 cells; EPO, eosinophil peroxidase; FDP, fibrin degradation products; FXa, factor Xa; GM-CSF, granulocyte–macrophage colony-stimulating factor; HR, histamine receptors; MBP, major basic protein; MPO, myeloperoxidase; MRGPRX2, Mas-related G-protein-coupled receptor X2; PAF, platelet-activating factor; PAR, protease-activated receptor; PGD_2, prostaglandin D2; SCF, stem cell factor; Siglec 8, sialic acid-binding immunoglobulin-like lectin 8; SYK, spleen tyrosine kinase; TNF, tumour necrosis factor; TSLP, thymic stromal lymphopoietin; VEGF, vascular endothelial growth factor.

Basic tests include a differential blood count and the erythrocyte sedimentation rate (ESR) and/or CRP in all patients with CSU, and measurements of IgG anti-TPO and total serum IgE levels in patients with CSU in specialist care. The latter two can help in the diagnosis of autoimmune CSU and elevated IgG anti-TPO levels point to concomitant autoimmune thyroiditis[7,40,113]. Further tests should only be performed if indicated by patient history and are rarely needed[4].

Chronic inducible urticaria. In patients with CIndU, wheals are often of shorter duration (≤1 h) than in those with CSU (up to 24 h)[4,106]. High-frequency trigger exposure and a low trigger threshold are linked to high disease activity[4,106]. Even though the lesions are usually confined to areas of skin exposed to the trigger stimuli, systemic reactions including anaphylaxis may occur and adrenaline autoinjectors should be prescribed to high-risk patients[114]. During pregnancy, one-half of patients experience improvement of their CU, whereas exacerbation occurs in approximately one-third of patients[115]. In particular, patients with CIndU or both CSU and CIndU showed a twofold increase of disease exacerbation during pregnancy. Disease activity changes during pregnancy might be linked to changes in trigger exposure and/or hormonal and immunological changes that promote mast cell activation.

The diagnosis of CIndU is based on a thorough history and the results of provocation testing. The aims of provocation testing are to determine the relevant triggers and to assess trigger thresholds, which are useful for measuring disease activity and monitoring treatment responses. For most CIndU subtypes, validated tools for provocation testing are available (TABLE 2; see Supplementary Table 9 and Supplementary Fig. 2).

Provocation testing
A method to confirm the diagnosis of chronic inducible urticaria (CIndU) using established protocols.

Comorbidities

Acute urticaria. Infection, mainly upper respiratory tract infection, is considered the most common comorbidity and aetiological factor of acute spontaneous urticaria (~30–40% of AU cases), although the prevalence of infectious aetiologies decreases as the age of patients increases (see Supplementary Table 4). Less frequently, reactions can be triggered by drugs, mostly NSAIDs and antibiotics, inhalant allergens (for example, pollen, dust mites), foods, stress, *Hymenoptera* stings and physical factors (see Supplementary Table 4). Drugs such as NSAIDs are often used when infection is present, and this makes it challenging to differentiate between medications or infection as the cause of urticaria. Inducible factors are considered to be a rare cause of AU in children but can lead to AU in <15% of all adult AU cases[116] (see Supplementary Table 4). The cause of AU was more frequently detected in patients 0–6 years of age than in those 7–18 years of age[51]. Foods and infection caused AU more often in children <13 years of age than in children 13–18 years of age[51]. AU usually disappears after resolution or eradication of infection, or avoidance of drugs and other causative triggers.

Chronic spontaneous urticaria. CIndU is a frequent comorbidity of CSU, with most studies reporting rates >10% (see Supplementary Table 6). Among patients with CU, 29–93% had CSU only, 6–35% had CIndU only and 1–43% had both CSU and CIndU (see Supplementary Table 6). Of 245 patients with CSU, 36% had CIndU confirmed by a positive challenge test, mostly symptomatic dermographism (25%) and ColdU (13%)[48]. Multiple types of CIndU may coexist in the same patient with CSU[117].

Autoimmune diseases are present in 28% of patients with CSU, most frequently autoimmune thyroid diseases (~25%, mostly Hashimoto's thyroiditis with or without hypothyroidism), vitiligo, rheumatoid arthritis, autoimmune gastritis and diabetes mellitus (1–2%)[40,118].

Bacterial infection including *Helicobacter pylori* and focal bacterial infections, for example dental infection, have been reported in up to 77% of patients with CSU[5]. However, the evidence for the causal link between bacterial infection and CSU development is still weak and conflicting[5]. The clinical relevance of viral infection, for example viral hepatitis and HIV infection, and fungal infection is still unknown and these infections are unlikely to contribute to the development of CSU[5]. In one study, CU did not affect the course of COVID-19, whereas COVID-19 induced CU exacerbation in one-third of patients, especially in patients with severe COVID-19 (REF.[119]). CSU improved in one-third of patients after the treatment of confirmed infection with helminths or protozoa with antiparasitic drugs, although the link between CSU and parasites is still ill-characterized[5].

The evidence for the increased prevalence of allergic diseases in patients with CSU is inconsistent[5].

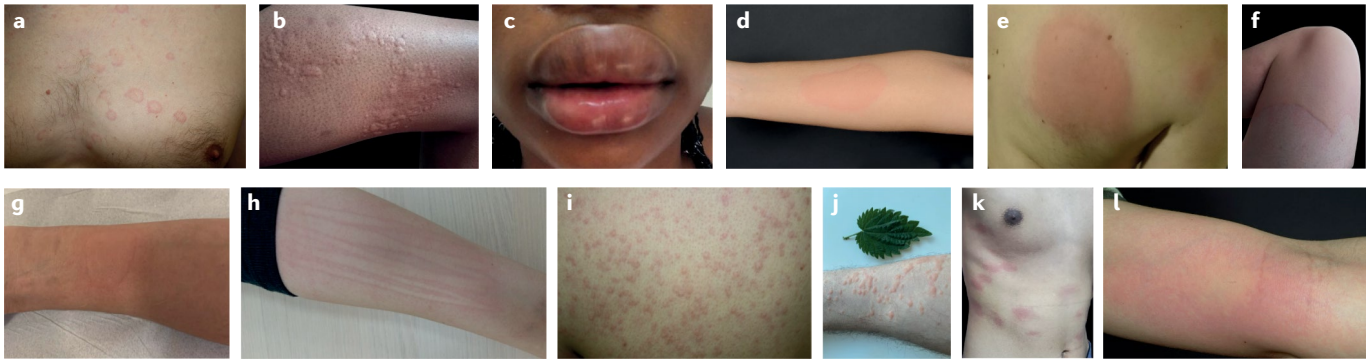


Fig. 4 | **Clinical manifestations of urticaria. a** | Acute urticaria (AU). **b** | Chronic spontaneous urticaria (CSU) (wheals). **c** | CSU (angioedema). **d** | Cold urticaria (ColdU). **e** | Delayed pressure urticaria. **f** | Solar urticaria. **g** | Heat urticaria. **h** | Symptomatic dermographism. **i** | Cholinergic urticaria (CholU). **j** | Contact urticaria. **k** | Aquagenic urticaria. **l** | Vibratory angioedema. Part **e**, image courtesy of A. Kasperska-Zajac. Part **g**, image courtesy of L. F. C. Ensina. Part **l**, image courtesy of K. Brockow.

Three large studies suggest that individuals with CSU are considerably more likely to have allergic diseases compared with the general population or control subjects without urticaria[34,120,121]. Type I hypersensitivity to allergens as a cause of CSU should be ruled out in patients with intermittent symptoms, a temporal relationship to a particular allergen and possible symptoms due to other allergic diseases, for example asthma.

Cancer, mostly non-haematologic, was reported in 0–9% of patients with CSU[5,26] and CSU resolved in some cases once patients were in remission[122]. CSU development in patients with cancer might be related to cancer-induced immune dysregulation including activation of complement and coagulation cascade[123], and return to normal homeostatic conditions might parallel CSU improvement after cancer treatment. Mental health disorders, mainly depression and anxiety, are present in up to 60% of patients with CSU and are associated with considerably impaired quality of life[5]. Prevalence of one or several components of metabolic syndrome, that is, central obesity, dyslipidaemia, hyperglycaemia and hypertension, was considerably increased in patients with CU including CSU compared with control subjects without CU/CSU[5].

Chronic inducible urticaria. CIndU can coexist with CSU and other CIndU forms. CSU was reported in 71%, 25% and 10% of patients with symptomatic dermographism[124], CholU[125] and ColdU[114], respectively. Among patients with CU, symptomatic dermographism alone or in combination with CSU is more prevalent than other CIndU, followed by ColdU and CholU (see Supplementary Table 6). Allergic diseases were reported to be a frequent comorbidity (up to 26–48%) of CholU[126], solar urticaria[127], ColdU[128] and symptomatic dermographism[129].

Differential diagnosis

Patients with certain diseases other than urticaria can present with wheals and/or angioedema as associated or prodromic signs[130] (FIG. 5; see Supplementary Table 10). The differential diagnoses of CSU are guided by the history and physical examination and supported by exploratory tests.

In patients who exclusively develop wheals but not angioedema, autoinflammatory disorders, such as Schnitzler syndrome or cryopyrin-associated periodic syndromes, should be considered differential diagnoses[4]. Wheals in patients with autoinflammatory disorders are refractory to antihistamines and can present a distinct entity called neutrophilic urticarial dermatosis with a dense perivascular and interstitial infiltrate of neutrophils with leukocytoclasia but without vessel wall necrosis[131].

In urticarial vasculitis, both long-lasting wheals (>24 h) and angioedema can occur and the diagnosis is confirmed by a combination of three histological criteria: leukocytoclasia, fibrin deposits and extravasated erythrocytes[132,133]. By contrast, CSU histopathology usually shows dermal oedema with an inflammatory infiltrate consisting of lymphocytes, eosinophils, neutrophils and nuclear dust, without evidence of vasculitis[60,132].

When patients show recurrent angioedema without wheals, bradykinin-mediated angioedema including angiotensin-converting enzyme inhibitor-induced angioedema and hereditary angioedema should be excluded[4].

Disease activity and control

Several patient-reported outcome measures, global and validated tools, were developed to assess CU activity and control and are used both in clinical care and in trials[134] (BOX 1). The Urticaria Activity Score (UAS) is a gold standard to assess disease activity (wheals number and itch intensity) in CSU and is usually used prospectively during seven consecutive days (UAS7)[4,135]. Similarly, the Angioedema Activity Score (AAS) is a prospective, diary-type tool that enables clinicians to measure angioedema activity in patients with all forms of recurrent angioedema[136]. In CIndU, the Cholinergic Urticaria Activity Score (CholUAS; not yet validated) and the Cold Urticaria Activity Score (ColdUAS), modified versions of the UAS, collect data on a daily basis assessing the intensity of wheals and pruritus as well as the intensity of exposure to specific triggers with a recall period of 24 h[134,137,138]. The Urticaria Control Test (UCT)[139] and the Angioedema Control Test (AECT)[140] are retrospective tools with a recall period of 4 weeks used to assess disease control in all forms of CU.

GRADE methodologies (Grading of Recommendations Assessment, Development and Evaluation methodologies). A transparent framework for rating the quality of evidence and grading the strength of recommendations.

Screening

No screening methods are available for urticaria in the general population. Patients with autoimmune diseases, especially autoimmune thyroiditis, should be asked for signs and symptoms of CSU[40,42,118]. Similarly, patients with CSU should be regularly checked for autoimmune thyroid disease by palpation of the thyroid, thyroid function tests and anti-TPO and anti-thyroglobulin antibodies[4,40,118].

In CSU, basic screening tests (differential blood count, ESR and/or CRP) and screening tests performed in specialist care (total IgE and IgG anti-TPO) can help in identifying comorbid and underlying diseases, for example chronic infection, autoimmune disease and allergy, as well as differential diagnoses, for example urticarial vasculitis or autoinflammatory disorder[4]. Mental health disorders, namely depression and anxiety, common comorbidities and consequences of CSU should be checked for in every patient with CSU[4].

Prevention

No primary prevention exists for urticaria with the possible exception of allergic urticaria, in which general preventive measures for allergic diseases may apply (especially in children with high risk of allergy). A population-based cross-sectional study in China found that breastfeeding >6 months after birth can lower the risk of urticaria[33]. Secondary prevention measures include avoidance of exposure to a relevant trigger, for example wearing of tight-fitting clothes by a patient with delayed pressure urticaria or intake of particular food or drug by a patient with allergic urticaria[4]. Migration to different geographic regions with different ambient temperatures might decrease the risk of development of CIndU such as ColdU. Finally, tertiary prevention is possible with treatment of symptoms using guideline-recommended options, for example antihistamines and omalizumab[4], and might be possible with induction of long-lasting remission with disease-modifying treatments, for example allergen-specific immune therapy in patients with allergic urticaria[84], cyclosporine in patients with autoimmune CSU[141,142] and novel mast cell-reducing therapies[143].

Management

The management of urticaria has progressed substantially over the past two decades, with disease control possible for at least two-thirds of patients[144–146]. Increased understanding of disease pathogenesis underpins an expanding pipeline of targeted therapies with improved adverse effect profiles compared with traditional immunosuppressants (TABLE 3). Structured assembly of the evidence for pharmacological and non-pharmacological agents using GRADE methodologies (Grading of Recommendations Assessment, Development and Evaluation methodologies), together with publication

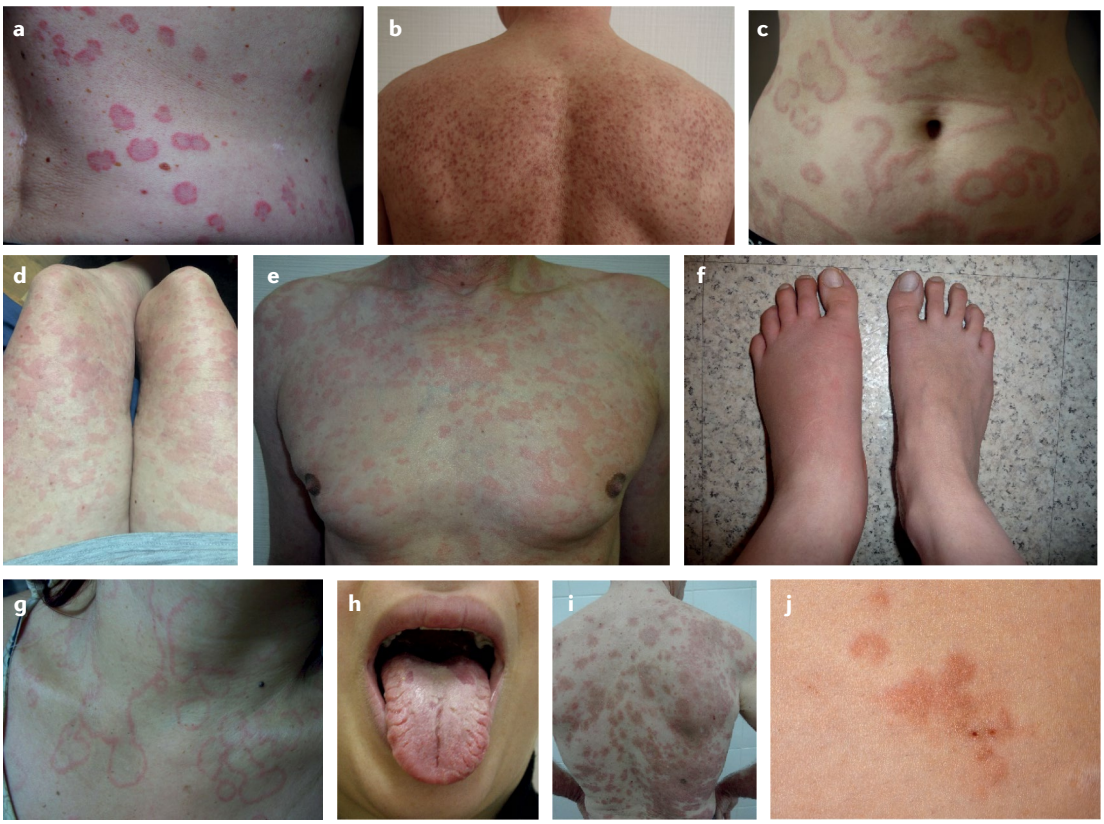


Fig. 5 | **Differential diagnosis of urticaria. a** | Urticarial vasculitis. **b** | Mastocytosis in the skin. **c** | Erythema annularis centrifugum. **d** | Cryopyrin-associated autoinflammatory syndrome **e** | Schnitzler syndrome. **f** | Hereditary angioedema. **g** | Erythema marginatum in a patient with hereditary angioedema. **h** | Melkersson–Rosenthal syndrome (oedema of the upper lip and fissured tongue are seen). **i** | Erythema multiforme. **j** | Hypereosinophilic syndrome.

Box 1 | **Established disease-specific instruments to assess activity and control of chronic urticaria and patient quality of life**

Disease activity

- Urticaria Activity Score (UAS)[4,135]
- Angioedema Activity Score (AAS)[136]
- Cholinergic Urticaria Activity Score (CholUAS)[138]
- Cold Urticaria Activity Score (ColdUAS)[137]

Disease control

- Urticaria Control Test (UCT)[139]
- Angioedema Control Test (AECT)[140]

Patient quality of life

- Chronic Urticaria-Quality of Life Questionnaire (CU-Q_2oL)[223]
- Angioedema-Quality of Life Questionnaire (AE-QoL)[225]
- Cholinergic Urticaria-Quality of Life Questionnaire (CholU-QoL)[224]

of up-to-date international consensus guidelines, has led to the establishment and regular review of an international standard of care for urticaria[4]. The overall goal of treatment is safe and effective attainment of complete disease control (UAS7 = 0 and UCT = 16) with a normal quality of life. FIGURE 6 provides the current consensus algorithm for urticaria treatment[4].

Elimination of causes and avoidance of triggers

AU or CSU with an intermittent–recurrent course with an identifiable exogenous trigger, for example an NSAID, is effectively managed with avoidance of the trigger and cross-reacting molecules[4,147]. Inducible urticaria, by definition, has an eliciting factor, or group of factors, and exposure reduction methods are a mainstay of therapy; however, avoidance might be hard to achieve, for example avoiding cold ambient temperatures, or might negatively affect quality of life[4]. Autoimmunity underlying CSU cannot be eliminated, although direct autoantibody removal through plasmapheresis has been successful, with high financial cost, in a limited number of patients with severe treatment resistance[148,149]. Removal of inciting antigens, either spontaneously (for example, resolution of an acute viral or bacterial infection) or through treatment of an underlying condition (for example, solid cancer surgery), can lead to resolution of urticaria[122]. Disappointingly, especially in CU, the treatment of underlying or associated factors often fails to alter the trajectory of CU. Eradication therapies for chronic infections, such as *H. pylori*, are a good example, and an analysis of studies based on the GRADE approach demonstrated weak and conflicting evidence between *H. pylori* eradication and improvement of CU[150]. Thyroid supplementation or anti-thyroid drugs in patients with CSU with Hashimoto's thyroiditis or Graves' disease, respectively, is another example when associated disease treatments have limited efficacy in reducing urticaria[118,151]. In most of these instances, no randomized controlled trial data are available and the evidence quality is low[4,151]. Thus, the intensive and costly general screening programmes for causes of CSU should not be performed, unless indicated by the patient's clinical history, physical examination and/or initial CSU workup. In addition, the treatment of associated thyroid autoimmunity and other comorbidities should be individualized and based on disease-specific complications, for example hypothyroidism[4].

Second-generation H1 antihistamines

Multiple effective and affordable second-generation antihistamines (sgAHs) that block the H_1 receptor are available and are the standard and first step in urticaria treatment[152,153]. They do not antagonize the binding of histamine but act as inverse agonists and have the opposite effect on the receptor to histamine, therefore shifting the equilibrium towards the inactive state[154]. Most guidelines recommend against the use of first-generation H1-AH due to sedative and anticholinergic effects, and drug–drug interactions[4,155]. Most, but not all, sgAHs have been evaluated and shown effective in urticaria at standard doses[4]. Studies have also confirmed the safety and efficacy of using off-label high-dose sgAH therapy (up to fourfold the recommended daily dose), including for bilastine, cetirizine, desloratadine, ebastine, fexofenadine, levocetirizine and rupatadine[145,156–160] However, the use of updosed sgAHs is associated with a higher risk of somnolence than the use of standard dose of sgAHs (relative risk 3.28; 95% confidence interval 1.55–6.95; $p = 0.002$)[161]. Of note, British urticaria guidelines from 2021 recommend against updosing on mizolastine[162]. High-dose sgAHs are now considered part of the first step in urticaria treatment, if the standard dose is not sufficient to control symptoms[4]. The optimal timing and approach to step up or step down antihistamine therapy are still based on expert opinion, and include both tapering or immediate discontinuation. Based on half-life considerations, a 2-week period is generally considered sufficient to observe the effect of antihistamine changes in CU[163].

Around 61% of patients with CSU do not respond to the licensed doses of sgAHs and only ~63% of these non-responders benefit from updosed sgAHs[145]. The second-line therapy with omalizumab as an add-on to sgAHs is indicated in patients with CSU who do not respond to increased doses of sgAHs[4].

Omalizumab

Omalizumab is the first in-class anti-IgE monoclonal antibody (mAb) and binds and lowers free IgE, with subsequent downregulation of FcεRI on basophils and mast cells[164–167]. Lowered FcεRI expression may render the cells less susceptible to activation by IgE and IgG anti-FcεRI and prevent histamine release and inflammation[167]. As the step-up treatment from antihistamines, omalizumab, as an add-on therapy, has the strongest evidence base and recommendations of all possible treatments for CSU in patients ≥12 years of age[146]. A meta-analysis of 67 real-life CSU studies reported complete and partial response rates of 72% and 18%, respectively, comparable with efficacy in clinical trials, with a mean adverse effect rate of 4%[168]. Omalizumab improves various aspects of quality of life in patients with CSU in both clinical trials and real-life studies[169–171]. It has also been shown to be effective (although has not yet been approved) in the management of CIndU, particularly symptomatic dermographism, ColdU, CholU and solar urticaria[166,172–175].

Table 3 | **Potential molecular targets, candidate drugs and clinical trials in chronic urticaria**

Drug	Target	Type	Route	Urticaria type	Phase	ClinicalTrials.gov identifier
MTPS9579A	Tryptase	mAb	IV	CSU	II	NCT05129423
Etanercept	TNF	FP	SC	CSU	II–III	NCT01030120
Canakinumab	IL-1β	mAb	SC	CSU	II	NCT01635127 (REF.[256])
Rilonacept	IL-1β, IL-1α	FP	SC	ColdU	II	NCT02171416
Dupilumab	IL-4Rα	mAb	SC	CSU	II–III	NCT03749135–NCT04180488
				CholU	II	NCT03749148
				ColdU	III	NCT04681729
Benralizumab	IL-5Rα	mAb	SC	CSU	II	NCT04612725
					IV	NCT03183024 (REF.[215])
Mepolizumab	IL-5	mAb	SC	CSU	I	NCT03494881
LEO 152020	H4R	SM	Oral	CholU	II	NCT04853992
AZD1981	CRTh2	Antagonist	Oral	CSU	II	NCT02031679 (REF.[257])
Vixarelimab	IL-31 (via OSMRβ)	mAb	SC	CSU	II	NCT03858634
Ligelizumab	FcεRI (via IgE)	mAb	SC	CSU	II	NCT02649218
						NCT02477332 (REF.[207])
					III	NCT03580356
						NCT03580369
						NCT04210843
						NCT03907878
				CSU, CholU, ColdU	I	NCT04513548
				CIndU	III	NCT05024058
UB-221	FcεRI (via IgE)	mAb	IV	CSU	I	NCT03632291
						NCT04175704
						NCT04404023
					II	NCT05298215
UCB8600	FcεRI (via IgE)	mAb	Oral	CSU	I	NCT04444466
Tezepelumab	TSLP	mAb	SC	CSU	II	NCT04833855
Fenebrutinib	BTK	SM	Oral	CSU	II	NCT03137069 (REF.[209])
						NCT03693625
Remibrutinib	BTK	SM	Oral	CSU	II	NCT03926611
						NCT04109313
					III	NCT05048342
						NCT05032157
						NCT05030311
Rilzabrutinib	BTK	SM	Oral	CSU	II	NCT05107115
TAS5315	BTK	SM	Oral	CSU	II	NCT05335499
Tirabrutinib	BTK	SM	Oral	CSU	II	NCT04827589
GSK2646264	SYK	SM	Topical	CSU, ColdU	I	NCT02424799 (REF.[258])
LY3454738	CD200R	mAb	IV	CSU	II	NCT04159701
Lirentelimab	Siglec 8	mAb	IV	CSU, CholU, symptomatic dermographism	II	NCT03436797 (REF.[217])
Barzolvolimab	KIT	mAb	IV	CSU	I	NCT04538794
					II	NCT05368285
				ColdU, CholU, symptomatic dermographism	I	NCT04548869
Rituximab	CD20	mAb	IV	CSU	I–II	NCT00216762

BTK, Bruton's tyrosine kinase; CholU, cholinergic urticaria; CIndU, chronic inducible urticaria; ColdU, cold urticaria; CRTh2, chemoattractant receptor-homologous molecule expressed on T helper 2 cell (T_H2 cell); CSU, chronic spontaneous urticaria; FP, fusion protein; IV, intravenous injection; mAb, monoclonal antibody; OSMRβ, oncostatin M receptor-β; SC, subcutaneous injection; Siglec 8, sialic acid-binding immunoglobulin-like lectin 8; SM, small-molecule drug; SYK, spleen tyrosine kinase; TNF, tumour necrosis factor; TSLP, thymic stromal lymphopoietin.

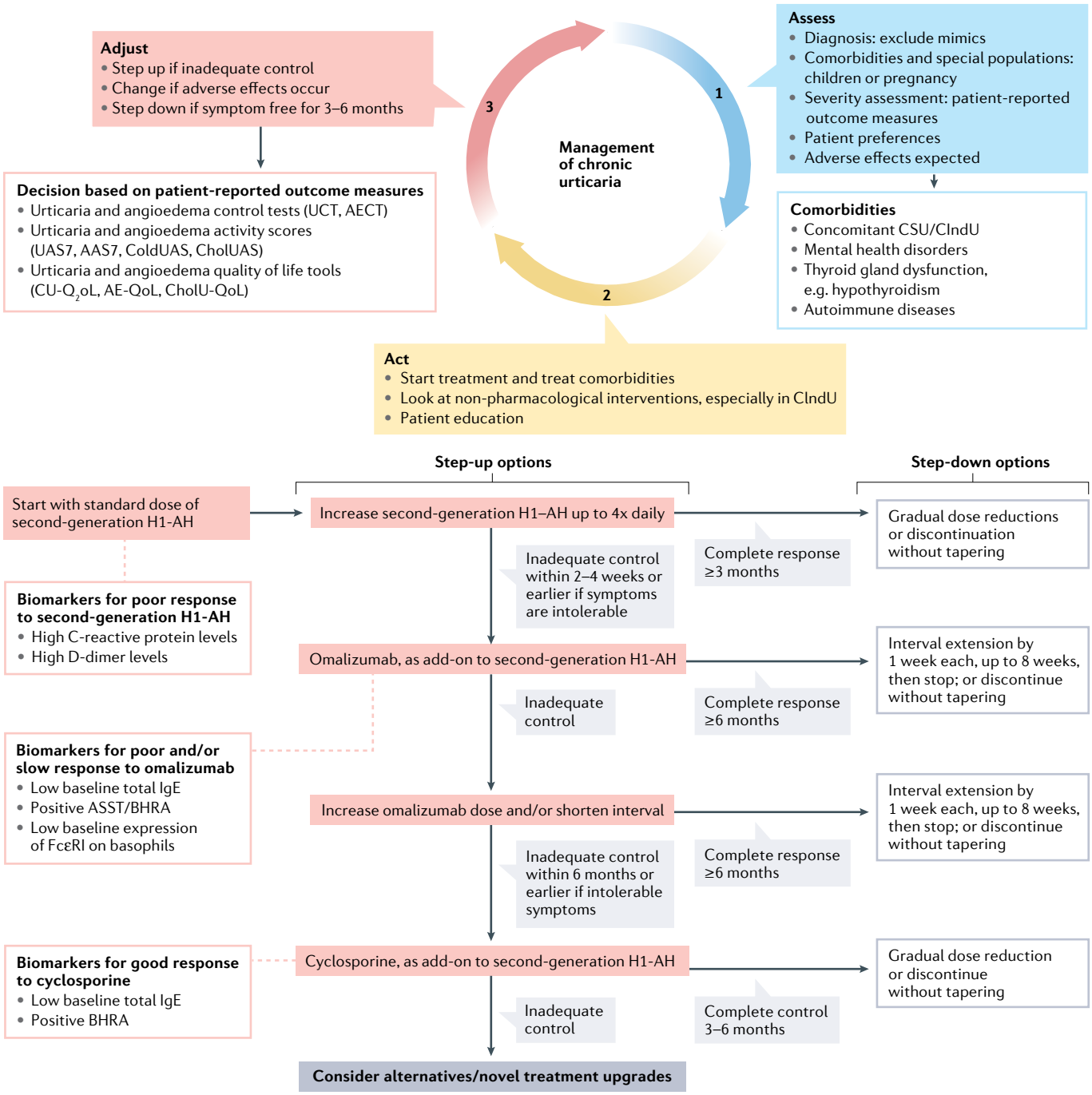


Fig. 6 | **Algorithm of chronic urticaria treatment.** The 3A management approach of assess, act and adjust recognizes the importance of several comorbidities associated with urticaria; and the wide range and dynamic nature of disease severity across time, with the need to step up and step down therapies to achieve complete disease control while limiting cost and adverse effects. Only some biomarkers of response to treatment are shown[246,259] and other biomarkers are listed in Supplementary Box 1. AAS7, Angioedema Activity Score used prospectively during 7 consecutive days; AECT, Angioedema Control Test; AE-QoL, Angioedema-Quality of Life Questionnaire; ASST, autologous serum skin test; BHRA, basophil histamine release assay; CholUAS, Cholinergic Urticaria Activity Score; CholU-QoL, Cholinergic Urticaria-Quality of Life Questionnaire; ClndU, chronic inducible urticaria; ColdUAS, Cold Urticaria Activity Score; CSU, chronic spontaneous urticaria; CU-Q_2oL, Chronic Urticaria-Quality of Life Questionnaire; H1-AH, H1 antihistamines; UAS7, Urticaria Activity Score used prospectively during 7 consecutive days; UCT, Urticaria Control Test. Adapted with permission from REF.[4], Wiley.

Poor and/or slow response to omalizumab was linked to several markers and features of autoimmune CSU, including BHRA positivity and low total IgE levels (see Supplementary Box 1).

Real-world practice continues to raise several questions around omalizumab use as monotherapy (without antihistamines): the initial treatment duration, updosing or a shortened dosing interval and discontinuation

strategies[176]. Alternative approaches include combination therapy with other systemic immunosuppressives (cyclosporine, dapsone and colchine), although evidence is very limited, or a complete switch to cyclosporine, a third-line treatment of CU[4,164,177,178].

Cyclosporine

Cyclosporine is a T cell immunosuppressive agent that also inhibits mediator release from basophils and mast cells[179]. It has been used for more than three decades for the treatment of CU[180]. Current guidelines recommend off-label use of cyclosporine as an add-on to sgAHs for patients with CSU with severe disease that is refractory to the combination of high-dose antihistamine and omalizumab[4]. Efficacy has been demonstrated in placebo-controlled randomized control trials[180–182] and open-label studies[183], with meta-analysis data suggesting response rates up to 73%[182]. Adverse effects can be severe, particularly renal impairment, and occur in up to 50% of patients; hence, most guidelines do not recommend cyclosporine as standard treatment[4]. However, in many countries without access to omalizumab, cyclosprine is used as a step-up therapy from antihistamines, owing to a more favourable risk–benefit profile than long-term corticosteroid use[4].

Alternative and specific treatments

Intravenous or oral systemic corticosteroids are effective for AU, and for rapid control of severe disease flares in CSU[4]. Guidelines and experts recommend limiting oral steroid therapy to a maximum of 10 days using the lowest effective dose, due to severe adverse effects associated with long therapy duration[4]. Other immunosuppressant or immunomodulatory therapies were used in CSU with various success rates, including dapsone, colchicine, sulfasalazine, methotrexate, interferon, phototherapy, intravenous immunoglobulin and plasmapheresis[4,184]. Few of these approaches have been studied in well-designed randomized control trials, with most data published as case series; hence, all have a low-quality evidence base[4]. Some immune therapies have shown efficacy including anti-TNF in CSU and delayed pressure urticaria[185,186], and UVA, UVB and psoralen plus UVA (commonly termed PUVA) treatment in CSU, ColdU, CholU and symptomatic dermographism[187–189].

Evidence for other therapies, such as H2 antihistamines, leukotriene receptor antagonists, diets, such as a pseudo-allergen-free diet, and mast cell stabilizers also remains low[4]. However, subgroups of patients with CSU might benefit from specific approaches, for example the use of leukotriene receptor antagonists in patients who are aspirin-intolerant[4,190]. Tolerance induction can be useful in selected patients with ColdU, CholU or solar urticaria[191], but tolerance is lost without continuous daily exposure, making the therapy impractical for many patients, for example the need for daily cold baths or showers in patients with ColdU[4].

Treatment of special populations

Pregnant women, breastfeeding women, children and geriatric populations require special consideration in CSU. The over-the-counter use of first-generation antihistamines and sgAHs for allergic disease makes it likely that, at least, early pregnancy exposure to these drugs is common[4]. However, safety in pregnancy has been shown for cetirizine and loratadine only, and these drugs are therefore preferred[192,193]. The use of sgAHs such as loratadine and cetirizine is also advised in breastfeeding women[4], as nursing infants can develop sedation from first-generation antihistamines secreted into breast milk[194]. Omalizumab is reported safe in pregnancy[115,195–198] and in younger children, although current licensing is for individuals aged 12 years and older[146].

In the paediatric population, several sgAHs have proven efficacy and safety: bilastine, cetirizine, desloratadine, fexofenadine, levocetirizine, loratadine and rupatadine[4]. The individual choice should consider country-specific availability of suitable preparations, such as syrups.

The older population is particularly sensitive to adverse effects from first-generation antihistamines, which should be avoided[199]. Data have shown efficacy and safety of standard doses of sgAHs and omalizumab in older patients[199,200] (≥65 years old). However, older populations may be particularly susceptible to the sedative action of some sgAHs, such as cetirizine and loratadine, when recommended doses are exceeded[199]. Also, sgAHs updosing might cause risks in some older patients with renal, hepatic and/or cardiac disorders.

Risk–benefit profiles for immunosuppressive therapies, including corticosteroids and cyclosporine, need to be carefully considered given the increased toxic effects in all three of these patient populations. Detailed reviews of all aspects of CSU management in these groups are available[115,199,201–203].

Therapies in development

Various therapies, targeting mediators, receptors and signalling pathways of mast and other immune cells, are in preclinical and clinical development[13,164,204–206] (FIG. 3; all ongoing studies are listed in TABLE 3). Most therapies are focused on patients with antihistamine-refractory and/or omalizumab-refractory CSU.

Ligelizumab, a humanized anti-IgE mAb, had a greater affinity to IgE and showed higher efficacy than omalizumab in a phase IIb trial[207] but not in the phase III PEARL1 and PEARL2 trials[208].

Fenebrutinib, a selective, reversible, oral BTK inhibitor, improved CSU within the first week and demonstrated a substantial benefit in patients with antihistamine-resistant CSU including patients with circulating anti-FcεRI autoantibodies; however, reversible grade 3 liver enzyme abnormalities were observed[209]. Another BTK inhibitor, remibrutinib, provided improvements in UAS7 versus placebo, increased patient quality of life[210] and had a favourable safety profile[211]; a phase III trial is ongoing.

An anti-KIT mAb, barzolvolimab, was tested in CSU and CIndU[212]. In 95% of patients with antihistamine-resistant ColdU and symptomatic dermographism, a complete response (negative provocation testing) was observed after a single dose of barzolvolimab. Serum tryptase and skin mast cell depletion

mirrored barzolvolimab clinical activity. Similar effects of multiple-dose treatment with barzolvolimab were seen in patients with CSU[213] and a phase II study is ongoing. Barzolvolimab was generally well tolerated and most adverse effects were mild or moderate in severity including urinary tract infections, headache, neutropenia and back pain in patients with CSU[214] and hair colour changes, mild infusion reactions and transient changes in taste in patients with CIndU[212].

Benralizumab, an anti-IL-5Rα mAb, demonstrated sustained mean changes in UAS7 from baseline to week 24 in patients with CSU in a single-centre study: both components of the UAS7, pruritus severity and wheal size, decreased to a similar extent[215]. In a phase III trial, dupilumab, an anti-IL-4Rα mAb, reduced itch and wheals in patients with CSU who were omalizumab-naïve sgAH-resistant, but failed to meet primary end points in patients with poor response to omalizumab[216].

Lirentelimab, an anti-Siglec 8 mAb, increased UCT scores across cohorts of patients with CSU and CIndU, with complete response rates of 92%, 36%, 82% and 40% in patients who are omalizumab-naïve, patients who are omalizumab-refractory, patients with CholU and patients with symptomatic dermographism, respectively[217]. Secukinumab, an anti-IL-17 mAb, was effective in eight patients with CSU who were omalizumab-refractory, but onset of action was slow[218]. Other promising targets include tryptase, SYK, C5aR, MRGPRX2, IL-33, thymic stromal lymphopoietin (TSLP) and H4R; for some of them, drugs are already in development (TABLE 3 and FIG. 3).

Quality of life

The quality of life of patients with urticaria, especially CU, is often severely impaired, with marked physical, psychological, social and emotional effects[11]. Many different instruments are available for the assessment of quality of life impairment in patients with urticaria, ranging from generic questionnaires, such as the Short Form-36 (SF-36)[219] or the Nottingham Health Profile (NHP)[220], to organ-specific quality of life questionnaires, such as the Skindex-29 (REF.[221]) or the Dermatology Life Quality Index (DLQI)[222], to disease-specific instruments such as the Chronic Urticaria-Quality of Life Questionnaire (CU-Q_2oL)[223], Cholinergic Urticaria-Quality of Life Questionnaire (CholU-QoL)[224] and Angioedema-Quality of Life Questionnaire (AE-QoL)[225] (BOX 1). These questionnaires are available in validated form for many countries and languages, and the disease-specific questionnaires are recommended by the current international guideline on the diagnosis and treatment of urticaria for all patients with CU[4].

Owing to its short duration, AU has only a limited effect on patient quality of life, showing mean DLQI scores <1 for questions regarding social or leisure activities and personal relationships[226]. Patients with AU expressed greater satisfaction with life compared with patients with CU[227]. Patients with CIndU have a slightly better quality of life than patients with CSU, probably due to the transient nature of stimulus, whereas a combination of CSU and CIndU showed the highest DLQI scores, indicating the largest impact on quality of life[228].

The two most important drivers of quality of life impairment in CSU are the unpredictable course of the disease with the sudden onset of wheals and angioedema, and the severe pruritus. Consequences of pruritus in patients with CSU include lack of sleep, fatigue and lack of concentration[12,18,109,229,230]. Many patients with CSU suffer from daily or almost daily occurrence of the symptoms[4,231], which can lead to patients feeling loss of control over their lives[229]. The signs and symptoms of urticaria also result in embarrassment, frustration, sadness and anxiety in many patients[18,223,229]. These feelings are further exacerbated by the fact that the importance of urticaria is underestimated by others, including treating physicians[232,233]. In addition to reduced quality of life, CSU also leads to limitations in social interactions, work performance and functioning in daily life, including impairments in interpersonal relationships and sexual life[12,18,229,234,235].

Few direct comparisons of quality of life impairment in CU with other skin diseases exist. Independent studies with large numbers of patients in Europe and the USA have shown that quality of life impairment in CU is comparable with that in patients with moderate to severe psoriasis[18,236,237] and atopic dermatitis[236]. Compared with non-dermatologic conditions, social quality of life impairments in patients with CU were shown to be similar to those in patients with coronary artery disease who were about to undergo arterial bypass surgery[229] and worse than in patients with type I diabetes mellitus[238].

Untreated CU has substantial negative effects on patient quality of life, but response to therapy is associated with a corresponding improvement in quality of life: the more effective the therapy, the better the quality of life[239–242].

Outlook

Personalized treatment

AU is a disease with transient manifestations and without long-standing impairment of quality of life. However, for CU, no cure exists and the burden of disease is substantial. Future research should focus on the aetiology and pathogenesis of CU, which are currently poorly investigated and understood. Patients with CU often present with the same type of skin rash but differ in genotype, endotype and phenotype[38,91,243].

Genetic contributions to urticaria pathogenesis should be elucidated in high-throughput genetic studies, including whole-genome sequencing. Presence of comorbid diseases along with the phenotypes of CU subtypes are factors that contribute to the heterogeneity of the disease and can influence the variable therapeutic response and adverse effects to available drugs. Differences in CU phenotypes have been reported, including better response to antihistamines in patients with exclusive CIndU and less psychiatric comorbidities in patients with isolated CIndU or recurrent CSU[243]. Defining disease endotypes and their biomarkers is a major unmet need and will enable the identification of novel therapeutic targets, refine disease management via optimization of prevention and treatment with the available drugs, and assign newly developed drugs to those patients who will have the best benefit to risk ratio.

Box 2 | **Global variations in diagnosis and management of urticaria**

Approaches to the diagnosis and treatment of urticaria, as well as healthcare resource utilization, differ worldwide[260,261]. For example, patients residing in Europe compared with those in Central/South America have higher incidence of general practitioner visits and higher rates of controlled disease and treatment, including higher frequency of escalation to omalizumab[261]. This disparity can be explained by differences in awareness of the use of best available treatment options, differences in availability of diagnostic tests, treatment options and economic resources.

The mean time from chronic urticaria (CU) onset to proper diagnosis is ~2–4 years and considerably varies across countries[11,12,262]. Adherence to best-practice international urticaria guidelines has a direct affect on the quality of care of patients with urticaria and is associated with quicker diagnosis and treatment, and better treatment efficacy[12,260,263]. Approximately 60% of specialists follow international urticaria guidelines[260] and discrepancies in physicians' awareness of the guidelines among countries exist[263]. Although national and international urticaria guidelines usually agree on most points regarding urticaria management, some expert-based recommendations differ (mostly because of weak scientific evidence) that can also affect the final patient outcome[264].

One-fifth of physicians think that some of the guidelines' recommendations cannot be implemented in the physician's country of residency[260]. Availability of drugs and diagnostic tests, economic considerations, differences in coverage and payment for healthcare among different regions influence the choice of diagnostic and treatment strategies. Omalizumab is unavailable in some countries or its cost is high and not covered by health insurance programmes[265]; thus, systemic corticosteroids and first-generation H1 antihistamines (H1-AH), which are cheaper than omalizumab and second-generation H1-AH, may be preferred[263]. Similarly, some diagnostic tests, for example the basophil histamine release test and basophil activation test for diagnosis of autoimmune chronic spontaneous urticaria (CSU) or TempTest for diagnosis of cold and heat urticaria, are not standardized, are expensive and/or are available only at some urticaria centres, which may contribute to diagnosis delay[92].

Ultimately, this will also contribute to reducing healthcare costs, with improved quality of life for patients with CU. In this regard, mast cell, basophil and eosinophil activating factors have to be identified to better characterize the aetiology and pathogenesis of CU. For example, commercially available in vitro tests for detecting serum autoantibodies need to be developed.

A multi-omics approach, using data from genomics, transcriptomics and proteomics, can help identify relevant biomarkers to objectively measure characteristics of the disease. Reliable biomarkers, either alone or in combination, can help stratify patients with CU according to phenotypes and endotypes of disease, predict progression from AU to CU and measure disease activity, relapse and response to treatment, all of which would lead to a more precise treatment approach. Markers of CSU activity are already emerging, including increased levels of CRP, IL-6 and D-dimer[78,79,244]. The autoimmune endotype of CSU is associated with basopenia, eosinopenia, elevated IgG anti-TPO and low total IgE levels, which were linked to poor response to treatment with antihistamines and/or omalizumab. By contrast, higher baseline levels of total IgE were associated with better clinical responses to omalizumab[245], whereas low total IgE levels and a positive BHRA were linked to good response to cyclosporine[246]. Further promising markers exist (see Supplementary Box 1). Nevertheless, prospective multicentre studies are needed to further investigate these markers and identify new biomarkers, as well as to study pathogenesis in antihistamine-resistant urticaria and angioedema.

Drugs that failed to meet the primary end points in phase II/III trials in the classic one-size-fits-all approach may still be promising candidates in certain subpopulations of patients. Finally, drugs that have the potential to modify the disease course and induce sustained remission, especially in patients with CSU who are non-responders to sgAHs and omalizumab, are urgently needed.

Multidisciplinary approach including patients

A multidisciplinary approach should involve patients, dermatologists, allergists, rheumatologists, geneticists, pharmacologists, immunologists and researchers in these fields. Patient-reported outcome measures require more explicit recognition both in trials and in clinical practice. Specific quality of life instruments for ColdU, symptomatic dermographism and CholU already exist or are under development, but tools for the other forms of CIndU are missing and should be developed.

Patients with CU are interested in using mobile applications to monitor their disease activity and control[247]. For example, several mobile applications for the self-evaluation of CU and angioedema are available including UrCare, Urticaria, UrticariApp-Control Urticaria, SymTrac HIVES and TARGET My Hives[248]. However, existing mobile applications are limited in function and geographical reach[248]. The Chronic Urticaria Self Evaluation App (CRUSE) was developed in 2022 by the CRUSE core team and CRUSE advisory board, an international team of expert dermatologists and allergists, based on validated patient-reported outcome measures to help patients assess CSU activity and control and effects of CSU on quality of life. Patient's data can be sent directly to the treating physician and included in the Chronic Urticaria Registry (CURE). Initially launched in Germany, the CRUSE team aims to cover patients with CSU worldwide in the near future. Patients with CU are increasingly seeking information from information and communications technologies with web browsers being the preferred platform to obtain general health information[249], followed by email to contact physicians and WhatsApp for communicating with other patients[250]. The educational needs of patients can be addressed by urticaria-related websites and groups on social media, webinars and urticaria seminars.

Global approach

All urticaria stakeholders, including those in basic science, medical specialists, the pharmaceutical industry and health authorities together with patients, should contribute to creating solid evidence that enables identifying, managing and treating urticaria early with the aim of minimizing its effects on individuals and society. Awareness of up-to-date urticaria management should be increased worldwide to decrease diagnostic and therapeutic delays (BOX 2). Several global initiatives have been launched to address these objectives.

First, international guidelines for diagnosis and treatment of urticaria endorsed by 50 national and international societies from 31 countries are revised every 4 years[4]. Second, networks of Urticaria and Angioedema Centers of Reference and Excellence (UCARE and ACARE, respectively)[251,252] have been launched by

the Global Allergy and Asthma European Network (GA²LEN) with the aim to provide excellence in urticaria and angioedema management and to increase the knowledge of urticaria and angioedema through research and education. Third, the CURE[253] is the first international academia-driven registry to collect high-quality, real-life data on CU including patient characteristics, course of disease including cause, comorbidities, treatment response, quality of life impairment and healthcare data. Fourth, UCARE initiatives (UCARE LevelUp for physicians and UCARE 4U for patients) present up-to-date urticaria-related educational webinars. Finally, the Global Burden of Disease initiative can help assess urticaria prevalence, incidence and disability-adjusted life years[14]. However, as yet, these data do not differentiate between AU and CU, and therefore CU prevalence data for some countries and continents, for example Africa, are still lacking[14,22].

A global approach together with mobile health and personalized medicine should help implement prevention and control of urticaria in a cost-effective manner with each patient getting the best available treatment.

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Informed consent
The authors affirm that human research participants provided written informed consent for publication of the images in Figs. 1 and 4.

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