Received: 24 June 2020 | Revised: 13 November 2020 | Accepted: 18 November 2020

DOI: 10.1111/all.14674

Allergy EUROPEAN JOURNAL OF ALLERGY AND CLINICAL IMMUNOLOGY EAACI WILEY

REVIEW ARTICLE

Cold urticaria – What we know and what we do not know

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Abstract

Cold urticaria (ColdU) is a common form of chronic inducible urticaria characterized by the development of wheals, angioedema or both in response to cold exposure. Recent research and guideline updates have advanced our understanding and management of ColdU. Today, its pathophysiology is thought to involve the cold-induced formation of autoallergens and IgE to these autoallergens, which provoke a release of proinflammatory mediators from skin mast cells. The classification of ColdU includes typical and atypical subtypes. We know that cold-induced wheals usually develop on rewarming and resolve within an hour and that anaphylaxis can occur. The diagnosis relies on the patient's history and cold stimulation testing. Additional diagnostic work-up, including a search for underlying infections, should only be done if indicated by the patient's history. The management of ColdU includes cold avoidance, the regular use of nonsedating antihistamines and the off-label use of omalizumab. However, many questions regarding ColdU remain unanswered. Here, we review what is known about ColdU, and we present important unanswered questions on the epidemiology, underlying pathomechanisms, clinical heterogeneity and treatment outcomes. Our aim is to guide future efforts that will close these knowledge gaps and advance the management of ColdU.

KEYWORDS
cold stimulation testing, cold urticaria, cryoglobulinemic vasculitis, cryoglobulins, familial cold autoinflammatory syndrome

Abbreviations: CAPS, cryopyrin-associated periodic syndromes; CIndU, chronic inducible urticaria; ColdA, cold-induced anaphylaxis; ColdU, cold urticaria; COVID-19, coronavirus disease 2019; CRP, C-reactive protein; CryoVas, cryoglobulinemic vasculitis; CST, cold stimulation testing; CSTT, cold stimulation time threshold; CSU, chronic spontaneous urticaria; CTT, critical temperature threshold; DBPC, double-blind placebo-controlled; FACAS, FXII-associated cold autoinflammatory syndrome; FCAS, familial cold autoinflammatory syndrome; H1R, histamine H1 receptor; H2R, histamine H2 receptor; H4R, histamine H3 receptor; HIV, human immunodeficiency virus; HR, histamine release; IgE, immunoglobulin E; IgG, immunoglobulin G; IgM, immunoglobulin M; IQR, interquartile range; MC, mast cell; NIH, National Institute of Health; NLRP, NOD-, LRR- and pyrin domain-containing protein 3; NOD, nucleotide oligomerization domain; PLAID, phospholipase C-γ_2-associated deficiency and immune dysregulation; QoL, quality of life; RCT, randomized clinical trials; SD, standard deviation; sgAH, second-generation H_1-antihistamines; TNF-α, tumour necrosis factor-α; TRP, transient receptor potential; TRPA1, transient receptor potential ankyrin 1 cation channel; TRPM8, transient receptor potential melastatin-8 cation channel.

1 | INTRODUCTION

Cold urticaria (ColdU) is a subtype of chronic inducible urticaria (CIndU) characterized by wheals and/or angioedema that occur after cold exposure. ColdU is a challenging clinical problem, due to the risk of cold-induced anaphylaxis (ColdA), its long duration of several years on average and diagnostic difficulties with atypical ColdU. In recent years, much progress has been made in our understanding and management of ColdU, including the introduction of standardized Temp*Test* technology (Courage + Khazaka, Germany) in ColdU research. However, many questions related to the pathogenesis, the course and manifestations of the disease, comorbidities, predictive biomarkers, and the diagnosis and personalized treatment remain unanswered. The purpose of this work is to review our current understanding of ColdU and to outline unanswered questions regarding the epidemiology, the clinical heterogeneity, as well as the diagnosis and the management of ColdU (Table 1). We hope that this review will help to guide future

TABLE 1 Unanswered questions in ColdU research

	Category	Unanswered questions
1.	Definition and classification	How often does acute ColdU become chronic and what drives this progression?
		How many variants of atypical ColdU are there, and how are they characterized?
		Is it useful to distinguish primary and secondary ColdU, given the low level of evidence for the relevance of underlying causes of ColdU?
2.	Epidemiology	What is the point prevalence of ColdU across different geographical regions?
		What are the age range and the average age at disease onset and what is the prevalence of ColdU across age groups?
3.	Pathophysiology	What are the role and relevance of autoallergy in the pathogenesis of ColdU?
		Which autoantigens, including de novo autoantigens in the skin, are relevant for IgE-mediated MC activation in ColdU?
		Does IgG-mediated autoimmunity contribute to the pathogenesis of ColdU?
		What are the local events in the skin underlying a negative CST in ColdU patients?
4.	Clinical heterogeneity	What are the determinants of individual CTT and CSTT in ColdU patients?
		How can machine learning algorithms be used for clinical profiling of ColdU phenotypes?
		How is the QoL impaired in ColdU patients?
		What is the frequency of ColdA in typical and atypical ColdU?
		What is the fatality rate for ColdU?
5.	Comorbidities	What are the comorbidity patterns and the shared pathophysiology of ColdU with co-existing CIndU(s)?
		What are the characteristics of allergen sensitizations and comorbid atopic diseases in ColdU patients, with or without ColdA?
		What are the clinical severity and the frequency of ColdA in ColdU patients with or without atopy?
		What are the mechanisms underlying the interdependency[a] of ColdU and other CIndUs?
6.	Clinical course	What is the prevalence of ColdU with a duration of less than 6 wk?
		What is the rate of spontaneous remission in ColdU with a duration of less than 6 wk?
		What are the prognostic biomarkers for life-threatening or fatal ColdU?
		What are the predictive models for the risk of ColdA and for the disease severity in ColdU?
		What are the prognostic biomarkers for an early onset or a longer ColdU duration?
7.	Diagnosis	What is the optimal clinical grading of temperature thresholds in ColdU?
		What are the optimal diagnostic approaches to the patients with CTT below 4°C?
		What are the local events in the skin underlying a negative CST in ColdU patients?
		Are there altered thermoregulatory responses to cold provocations in ColdU patients?
8.	Laboratory testing	What is the clinical relevance of infections and cryoglobulins in ColdU?
9.	Differential diagnosis	What is the impact of systems biology and machine learning algorithms in the differential diagnosis of cold-induced urticarial rashes?
10.	Treatment	What are the effectiveness and a QoL impact of avoiding cold triggers on patient's QoL, severity and natural course of disease?
		What is the proportion of ColdU patients who can be effectively manage ColdU by cold avoidance?
		What are the prescription criteria for epinephrine in ColdU?
		What are predictive biomarkers for treatment efficacy in ColdU?
		What are the novel therapeutic targets in ColdU?
		How can ColdU patients be differentially managed based on their CST and CSTT?

[a]interdependency of cold and other triggers in ColdU (see Section 6).

efforts that will close these knowledge gaps and advance the management of ColdU.

2 | DEFINITION AND CLASSIFICATION

ColdU is characterized by itchy wheals, angioedema or both, with or without anaphylaxis, that occur in response to cooling of the skin and/or mucosa.[1] ColdU is defined as chronic when it persists for 6 weeks or longer. In this article, by using the term ColdU, we refer to chronic ColdU. Very little is known about acute ColdU, including its rates and the drivers of chronification.

ColdU was first described by Frank in 1792.[2] The early reports of ColdU date back to the mid-19th century.[3,4] In 1866, Bourdon reported a patient with urticaria and systemic symptoms following cold exposure.[3] Later on, Blachez reported a woman with hypersensitivity to cold objects and beverages.[4] In retrospect, these cases were typical ColdU according to the present classification of ColdU (Table 2).

Typical ColdU is characterized by cold-induced wheals that usually occur on rewarming and resolve within an hour.[1,5] In patients with typical ColdU, local whealing responses can be reproduced by cold stimulation testing (CST) using an ice cube or Temp*Test* technology (Figure 1).[1,6,7] By contrast, atypical ColdUs are characterized by either atypical cold-induced whealing or atypical CST responses or both (Table 2).[1,8-11] The variants of atypical ColdU include the following:

- Systemic atypical ColdU,
- Localized ColdU,
- Localized cold reflex urticaria,
- Delayed ColdU,
- Cold-induced cholinergic urticaria, and
- Cold-dependent dermographism.[12-25]

Some variants of atypical ColdU are extremely rare and therefore ill-characterized, underlining an unmet need to better classify atypical ColdU (Table 2).

Additionally, some authors classify ColdU into primary, that is idiopathic, and secondary, that is due to underlying causes such as autoimmune and lymphoproliferative diseases, viral and bacterial infections, Hymenoptera stings, intake of certain drugs or foods (Table 3).[26-31] However, the evidence for a causal relationship between these conditions and ColdU is weak, which calls into question the usefulness of this classification for clinical practice. Clearly, a better and clinically useful classification of ColdU should be developed, and more information on atypical forms of ColdU is needed (Table 1, Section 1).

3 | EPIDEMIOLOGY

The incidence of ColdU is estimated at 0.05%, with higher rates in cold-climate countries.[9,10] The exact point and lifetime prevalence of ColdU need to be established. ColdU is more frequent in women (Supplementary materials, Table S1).[6,28,32-39] ColdU can begin at any age, but mostly does so during the second to fourth decades of life (Supplementary materials, Table S1).[6,11,32,34,35,40,41] The trends for the incidence and prevalence of ColdU over time are unknown.

Overall, the demographics of ColdU patients remain uncertain (Supplementary materials, Table S1).[32-58] Geographical, gender and age differences in the prevalence of ColdU remain poorly defined (Table 1, Section 2). The ongoing COLD-CE study is the first global study to address these gaps of knowledge.

4 | AETIOPATHOGENESIS

What causes ColdU remains unknown. Current aetiopathogenic concepts consider autoallergy, autoimmunity, neurogenic pathways and aberrant temperature sensing as underlying mechanisms.

Exposure to cold may result in the de novo formation of autoantigens, which can induce an IgE response and, in sensitized individuals, subsequently leads to IgE-dependent mast cell degranulation and whealing (IgE-mediated autoimmunity).[59,60] As of now, no cold-dependent skin antigens have been identified, and direct evidence in support of this theory is lacking. It is, however, supported by several lines of indirect evidence (Table 4).[61-63] Although the initial events translating a cold stimulus into a sequence of molecular and cellular changes in the skin of ColdU patients remain obscure, this process in ColdU is likely to be immunologically mediated taking into account successful passive transfer studies in approximately 10%-50% of ColdU patients.[61,64,65] IgM-dependent passive transfer was occasionally reported, but in most cases, a passive transfer of ColdU to healthy recipients depended on IgE, as was demonstrated by a seminal study by Kaplan and associates,[61] or not mediated by any plasma components that could be identified.

Type IIb autoimmunity with mast cell-targeting and activating autoantibodies may also be involved. In nine ColdU patients, Gruber and colleagues first described IgG anti-IgE antibodies in five patients and IgM anti-IgE autoantibodies in two patients. Of these, only one patient had both classes of autoantibodies. In this study, the histamine-releasing effects of sera containing high titre IgM anti-IgE were shown to depend on either IgM or IgE fractions as demonstrated following passage over IgE sepharose or an anti-IgM immunoadsorbant but not IgG sepharose.[66] However, the clinical significance of these autoantibodies was questioned as there was a discrepancy between passive sensitization and basophil histamine release (HR) studies.[60]

There are limited data on skin autoreactivity and serum histamine-releasing activity in ColdU patients. Sera of five ColdU patients with skin autoreactivity (a positive autologous serum skin test, ASST) were shown to variably release histamine from basophils of two out of four healthy donors without any correlation with anti-IgE HR, suggesting the presence of circulating histamine-releasing factors that were active at body temperature in some ColdU patients.[67] Zuberbier and associates did not detect anti-FcεRIα autoantibodies

TABLE 2 The classification of ColdU

Category	Cold stimulation test (CST)		Urticarial response			
	Cold exposure	**Provocation time**	**Urticaria characteristics**	**Time of the reaction**	**Diagnosis**	**References**
Typical ColdU	Ice cube test Temp*Test*	0.5-20 min[6]	Whealing and itching at the area of CST	Immediately or within 5-15 min after cold exposure[6,8]	Cold (contact) urticaria	Neittaanmäki[6] Sibenhaar et al[7] Wanderer[8]
Atypical ColdUs	**1. Atypical CST with a typical urticarial response**					
	General body cooling at ambient 4°C temperature (cold room)[13,14]	10-20 min[12-14]	Localized or generalized whealing and/or angioedema or systemic reactions, often with hypotension	Immediately after cold exposure	Systemic atypical cold urticaria	Kaplan[12] Kivity et al[13] Wanderer[14]
	2. Typical CST with an atypical urticarial response					
	Ice cube test	5-20 min	Whealing occurs only if CST is carried out on certain areas (frequently on the face). No response can be elicited on other body parts.	Immediately after cold exposure	Localized cold urticaria	Kurtz et al[15] Mathelier-Fusade and Leynadier[16]
	Ice cube test	5-10 min	Multiple pinpoint/punctate pruritic wheals occur at the adjacent areas to the site of CST (at a distance of 5-8 cm). No systemic reactions reported.[19]	Immediately after cold exposure	Localized cold reflex urticaria	Czarnetzki et al[17] Ting and Mansfield[18] Wanderer and Hoffman[19]
	Ice cube test Iced water immersion	1-15 min (ice cube test)[22] 5-15 min (water immersion)[6,22]	Urticaria on uncovered cold-exposed areas and mucosal surfaces, angioedema affecting lips or oropharynx. No systemic reactions reported.[19]	9-72 h[6,21,22]	Delayed cold urticaria	Neittaanmäki[6] Wanderer and Hoffman[19] Soter et al[20] Bäck and Larsen[21] Sarkany and Turk[22]
	3. Atypical CST with an atypical urticarial response					
	Exercise in a cold environment (eg running followed by a cold room exposure at 4°C; or exercising in a cold room)	15 min (running) followed by 5−10 min in a cold room or a 15 min exercise in a cold room	Generalized pinpoint/punctate wheals (0,2 - 0,3 mm in diameter)	Immediately or within 10 min after cold exposure	Cold-induced cholinergic urticaria	Kaplan and Garofalo[23] Oda et al[24]
	Mechanical stroking of the skin before or during the cooling[20] Stroking of the precooled skin Scratching of the skin followed by a systemic cold exposure (a cold room, 4°C)[13]	5-8 min[12] (cold room)	Dermographic whealing (at the site of scratching or stroking) with or without generalized urticaria, angioedema or systemic reactions (nausea, diarrhoea, abdominal pain, hypotension)	Immediately or a few min after cold exposure	Cold-dependent dermographism	Wanderer[8] Kaplan[12] Wanderer and Hoffman[19] Matthews and Warin[25]

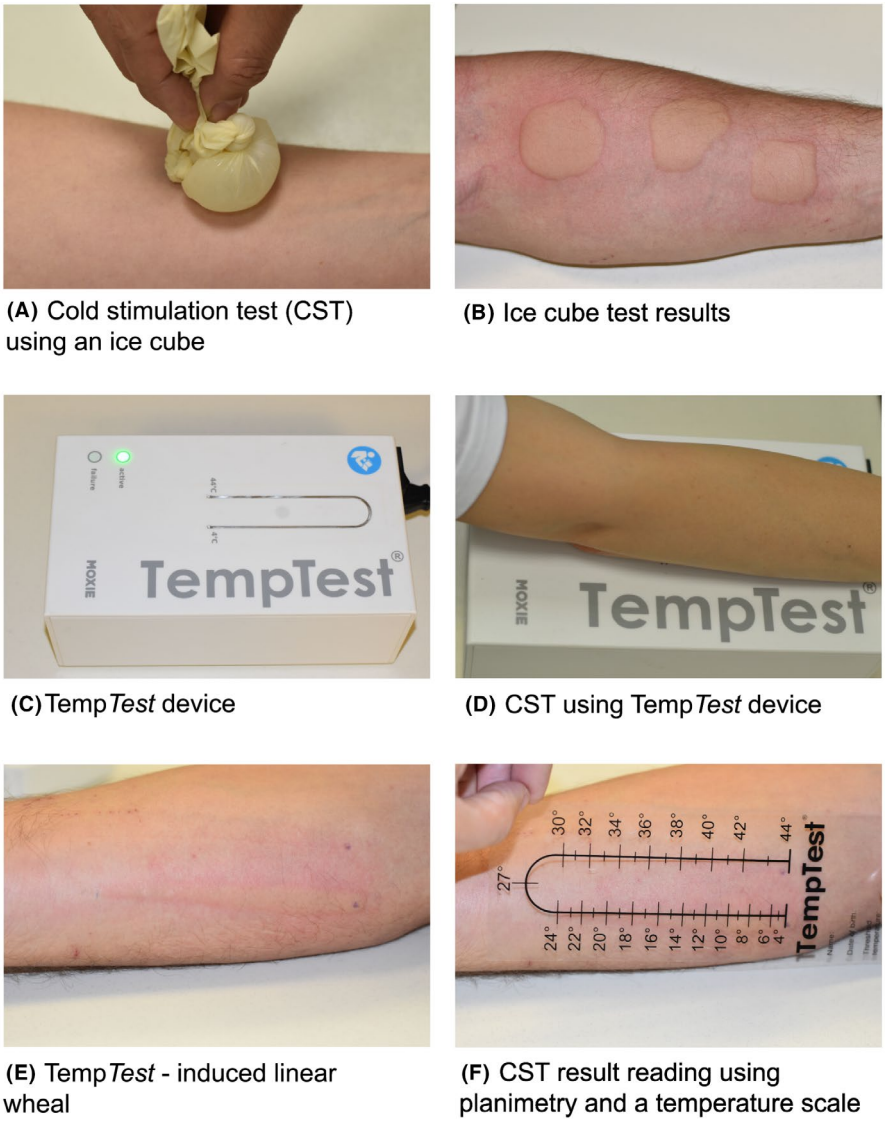

FIGURE 1 Cold stimulation tests (CSTs) in ColdU. CSTs in ColdU include ice cube testing or Temp*Test* testing (Courage + Khazaka, Germany). For ice cube testing, a melting ice cube in a plastic bag or in a non-latex medical glove is applied to the patient's volar forearm for 5 min (Figure 1A).[1] The ice cube results are read in 10 min (Figure 1B).[1] CST with Temp*Test* device (Figure 1C; Courage + Khazaka, Germany) is carried out on the patient's volar forearm (Figure 1D). Cold-induced whealing (Figure 1E) following Temp*Test* testing is measured using planimetry with a temperature scale (Figure 1F; the photos are a courtesy of Dr Mojca Bizjak)

in one tested ColdU patient.[68] Serum immunoreactivity to FcεRIa was demonstrated in one out of four tested ColdU patients although serum histamine-releasing activity was negative in all ColdU patients in this study.[69] Clearly, many questions regarding the aetiopathogenesis of ColdU remain unanswered, and the clarification of the contribution of IgE- and IgG-mediated autoimmunity, in our opinion, has high priority (Table 1, Section 3).

Other questions deal with the downstream mechanisms of dermal mast cell (MC) degranulation, the central event in ColdU whealing and angioedema formation.[70] The time course of HR in ColdU shows peak concentrations within minutes of cold provocation, which coincides with the onset of symptoms.[61] HR was demonstrated in the skin, blood, urine and suction blister fluid following a cold exposure.[71] In an in vitro model, upon challenge of skin biopsies from ColdU patients by exposure to different temperatures, there was a prominent augmentation of HR on chilling for 10 min and then rewarming to 37°C.[64] The kinetics and relevance of other mediators are less well defined. CST was reported to prompt the release of neutrophilic and eosinophilic chemotactic factors,[72,73] prostaglandin D_2 and tumour necrosis factor (TNF-α).[74-76]

On the other hand, basophil activation in ColdU is poorly understood. Kaplan demonstrated that basophil HR was not cold-dependent in ColdU.[64] Vonakis and colleagues showed that anti-IgE basophil HR in five ColdU patients was comparable to that in chronic spontaneous urticaria responders to anti-IgE stimulation and significantly higher than in non-responders.[69] SHIP-1 expression was decreased in ColdU patients and chronic spontaneous urticaria responders compared to healthy subjects but not to the level of hyperreleasable basophils.[69] Additionally, Hessler et al reported that, following a cold exposure, basophil HR to C5a stimulation and, to

TABLE 3 The potential causes and clinical associations of ColdU[8-10,19,26-31]

Infections	Viral (viral hepatitis A, B, C, Epstein-Barr virus, etc)
	Bacterial (Helicobacter pylori, Borrelia burgdorferi, Mycoplasma pneumoniae, Treponema pallidum, etc)
	Parasitic: helminths (Toxoplasma gondii, etc), protozoa (Giardia lamblia, etc), etc
Autoimmune diseases	Systemic lupus erythematosus
	Rheumatoid arthritis
	Sjögren's syndrome
	Autoimmune thyroiditis
	Scleroderma, etc
Lymphoproliferative diseases	Waldenström's macroglobulinemia
	Myeloma, etc
Drugs	Penicillin
	Combined oral contraceptives
	Angiotensin-converting enzyme inhibitors
	Anti-tetanus serum
	Griseofulvin, etc
Foods	High-protein meal such as beef
Insect stings	

TABLE 4 The summary of indirect evidence for IgE-mediated autoimmunity in ColdU

For	Against
Patients with another chronic urticarial condition (chronic spontaneous urticaria, CSU) show IgE reactivity to a wide range of autoantigens (Type I autoimmunity)[61]	The relevance of this finding for ColdU is unclear
Early mechanistic studies on immunoglobulins E and M (IgE and IgM) demonstrated a passive transfer of cold sensitivity (Prausnitz-Küstner reaction) by these serum factors from ColdU patients to healthy recipients[68]	The rate of successful passive transfer experiments ranged between 10% and 50%
Total serum IgE levels are elevated in up to 70% ColdU patients[9]	Total IgE levels or allergen-specific IgE levels to common allergens were not systematically studied in ColdU patients
The therapeutic monoclonal anti-IgE antibody omalizumab is effective in ColdU[66]	The precise mechanism of omalizumab action in ColdU remains unknown

a lesser extent to f-MMM, either declines (non-responders, n = 7) or remains unchanged (responders, n = 4).[77] Defective basophil HR in ColdU is likely to involve receptor-mediated pathways since the basophil HR to calcium ionophore was almost unaffected.[77] Besides, the lack of changes in basophil counts and basophil histamine content suggests that cold-induced alterations in basophil HR cannot be explained by in vivo activation of basophils.[77] Further studies are needed to define the activating mechanisms and signalling alterations in MCs and basophils in ColdU patients.

As of today, we do not know which factors modulate cold-induced whealing in ColdU (Table 1, Section 3). As in other CIndUs, dermal MC numbers appear to be normal in both lesional and non-lesional skin of ColdU patients.[78] Also, skin vessel reactivity to histamine was reported to be similar in ColdU patients and healthy controls.[79] Substance P is thought to modulate skin MC function by reducing the activation threshold.[80,81] Serum substance P levels were reported to be higher in ColdU patients compared to healthy subjects but lower than in chronic spontaneous urticaria (CSU) patients.[82] Although there was no evidence that mouse or human primary cultured MCs degranulate in response to cold or transient receptor potential (TRP) melastatin-8 cation channel (TRPM8) agonists,[83] transient receptor potential ankyrin 1 cation channel (TRPA1) and TRPM8 were demonstrated as cold sensors of the cutaneous microvasculature in animal models.[84] Thus, TRP channels may be involved in the aetiopathogenesis of ColdU, even though their relatively narrow temperature activation bands are not consistent with the wide range of clinically relevant temperatures in most ColdU patients.

Histologically, degranulated MCs and endothelial cell swellings without infiltrating leucocytes were noted throughout 24 hours after a single experimental cold challenge.[85] Mononuclear cell infiltrate was pronounced within 10 and 20 minutes in skin biopsies

from cold-provoked lesions in 10 ColdU patients, with scanty infiltrates of neutrophils and eosinophils.[86] By contrast, in the study by Winkelmann, in three out of five ColdU patients there was an inflammatory infiltrate with predominant neutrophils, indicating individual variations in skin histology.[87] In this respect, deficiency in α1-antichymotrypsin shown in one out of seven ColdU patients may suggest a possibility of insufficient control of neutrophil cathepsin G or mast cell chymase.[88,89] The role of eosinophils in ColdU is largely unknown, but eosinophil-targeted treatment with reslizumab can be of benefit for ColdU patients.[90] A prospective series of timed biopsies over 24 hours in six ColdU patients revealed no consistent changes in the cellular infiltrate at any time point.[70] Of note, sequential lesional skin biopsies from a ColdU patient showed upregulation of endothelial TNF-α and IL-3 expression within 30 minutes after an ice cube test.[91] The relative contribution of infiltrating cells, cytokines and their interactions in ColdU merit further research.

The role of cryoglobulins in skin MC activation in ColdU needs to be systematically investigated. Cryoglobulins are immunoglobulins that undergo a reversible precipitation at low temperatures and dissolve on rewarming.[92-94] Cryoglobulins are thought to activate complement components C3a and C5a and generate permeability, thereby mediating vessel damage in cryoglobulinemic vasculitis (CryoVas).[95] In ColdU, according to the study by Kaplan and colleagues, purified plasma IgE is functional as a monomer, does not polymerize in the cold, thus refuting the hypothesis of IgE cryoprotein.[64]

Overall, ColdU is an excellent experimental model disease for in vivo drug evaluations that can provide valuable mechanistic insights into wheal formation.[60,95,96] Antihistamine treatment with cyproheptadine resulted in a reduction of clinical symptoms without affecting HR in five of six patients; however, in one patient there was a significant HR reduction.[97] Prednisolone at an oral dose of 20-25 mg for 1-5 days was shown to suppress cold-induced HR in all but one ColdU patient, whereas the clinical response following prednisolone was unchanged suggesting that histamine cannot solely explain all vascular phenomena in ColdU.[98] Interestingly, topical application of capsaicin prevented cold-induced urticarial responses in seven ColdU patients for 4-7 days suggesting a role of nerve fibres in ColdU.[99] Despite a substantial progress in our understanding of ColdU, many important pieces of information are missing (Table 1, Section 3). Further progress can be made through systematic assessment of a cold-induced response at multiple levels by using well-established reproducible research models of ColdU. Careful interpretation of the integrated data may reveal novel insights on the aetiopathogenesis of ColdU.

5 | CLINICAL HETEROGENEITY

ColdU signs and symptoms may vary from local whealing to systemic symptoms including respiratory distress, hypotension with dizziness, nausea, diarrhoea, abdominal pain, disorientation and shock (Table 5).[6,11,41] The clinical presentation of ColdU depends on the potency and the duration of a cold exposure, individual cold sensitivity thresholds and other yet to be defined factors.

ColdU patients show a wide range of individual critical temperature thresholds (CTT), from below 4°C to higher than 27°C.[37] Common cold triggers include contact with cold objects or surfaces, cold water (eg swimming or taking cold showers), low ambient temperature (cold seasons, air conditioning), wind and the consumption of cold foods (ice cream, etc) and beverages. Although ColdU symptoms often worsen in winter, no seasonal variation was demonstrated in 60% of 30 patients by Siebenhaar *et al*[47] We still incompletely understand the effects of different relevant cold triggers on the clinical presentation of ColdU, as a detailed analysis of cold triggers has not yet been undertaken. Oropharyngeal angioedema may occur after ingestion of cold drinks or foods.[27,41,45] A high risk of ColdA is associated with the contact of extensive skin surface area with cold, for example, when swimming in open water,[100] and with administration of cool infusion solutions or prolonged surgical interventions[42,59,101] including hypothermic cardiopulmonary bypass surgery. Cold-induced Kounis syndrome, a coronary disorder, was reported in a ColdU patient after swimming in the sea.[102]

In ColdU, cold sensitivity can be characterized by CTTs and critical stimulation time thresholds (CSTTs).[1,103] CSTT is defined as the shortest time that is required to induce a wheal, whereas the CTT is

TABLE 5 Reported clinical presentations of ColdU

System	Symptoms
Constitutional symptoms	Fever,[6] fatigue[6]
Skin and mucous membranes	Itchy wheals[19] with or without angioedema affecting lips,[41] tongue,[6,19,41] pharynx[19,41]
Respiratory system	Dyspnoea,[6] hoarseness,[19] laryngeal angioedema,[10] nasal congestion[6]
Gastrointestinal tract	Nausea,[6] abdominal pain,[6] diarrhoea[19]
Cardiovascular system	Tachycardia,[6,19] hypotension,[41] shock[6]
Reproductive system	Uterine contractions[19]
CNS	Headache,[6,19] disorientation,[19,41] fainting,[6] vertigo[6]

the highest temperature that induces a wheal.[1] By use of Temp*Test* cold provocation testing (Figure 1, Section 8), CTTs were shown to correlate with patients' assessment of their ColdU severity.[37] In a study with 50 ColdU patients, a positive CSTT (using an ice cube) of 3 minutes or less was reported to be linked to a higher rate of severe systemic reactions after natural cold exposure.[11] In another study, ColdU patients with a history of oropharyngeal angioedema after consuming ice-cold foods and generalized urticaria with or without shock-like reactions after swimming in cold water demonstrated a positive CSST (using an ice cube) of less than 3 minutes.[41] Why patients differ in their CTTs and CSTTs and which factors govern these differences in thresholds remain unknown (Table 1, Section 4). Gender, age at disease onset, comorbid CSU and geographic area of residence are potentially influencing factors and are being explored in the ongoing COLD-CE study.

ColdA can fulfil any of the three diagnostic criteria according to current anaphylaxis practice parameters: a) sudden onset within minutes to several hours, with involvement of skin, mucosal tissue or both; b) two or more of the following occur suddenly after exposure to a likely allergen or other trigger for that patient (skin or mucosal symptoms or signs; respiratory symptoms, sudden reduced blood pressure or symptoms of end-organ dysfunction; gastrointestinal symptoms); c) reduced blood pressure after exposure to a known allergen for that patient.[104] However, the dependency of ColdA on the exposed area and the exposure time[8] suggests dose dependency, which is not a feature of classical IgE-mediated anaphylaxis. Although tryptase release was reported in ColdA, its utility in ColdA diagnosis needs further research.[105] The rate for ColdA ranges from 4% to 52% across studies (Supplementary material, Table S1).[6,11,28,32,35,36,40,41,47,50,106] In 1986, Wanderer and co-workers reported a ColdU severity grading based on the clinical data of 50 patients and their responses after natural cold exposure: (a) local reactions (wheals and angioedema), limited to the contact area with a cold trigger (type I) – 30%; (b) wheals and/or angioedema with involvement of another organ, except the cardiovascular system (type II) – 32%; and (c) generalized wheals and/or angioedema associated with systemic reactions such as hypotension, dizziness, syncope, disorientation (type III) – 38%.[11] However, the qualitative assessment is the limitation to this grading system, hence, the quantitative Acquired Cold Urticaria Severity Index (ACUSI) has been developed.[47] How disease severity is linked to quality of life (QoL) impairment in ColdU needs to be explored (Table 1, Section 4).

Importantly, there is no data on the fatality rate in ColdU (Table 1, Section 4). It remains unknown whether the risk of ColdA differs between typical and atypical ColdU (Table 1, Section 4). Of ten patients with atypical ColdU, eight had systemic reactions as reported by Wanderer and colleagues.[11] However, direct comparisons are lacking.

In the future, international registries such as the chronic urticaria registry (CURE; www.urticaria-registry.com) and machine learning approaches may help to better characterize the clinical heterogeneity of ColdU (Table 1, Section 4).

6 | COMORBIDITIES

Reported ColdU comorbidities include atopic diseases, other CIndUs and CSU (Supplementary materials, Table S1). In a retrospective study, 78% of 415 ColdU children had a history of atopic diseases.[42] In a study by Neittaanmäki,[6] 25% of patients with ColdU had atopic diseases, comparable to the prevalence in the general population. Of interest, atopic comorbidity was linked to more persistent ColdU.[34] How atopy and ColdU are linked is unknown (Table 1, Section 5).

ColdU may coexist with other CIndUs.[8] For example, 21% and 22% of ColdU patients also had symptomatic dermographism, and 8% and 10% also had cholinergic urticaria, in two retrospective studies.[6,33] Coexistence of ColdU and solar urticaria or aquagenic urticaria was also reported.[107,108] CIndU comorbidity needs to be distinguished from CIndU interdependency, that is the occurrence of wheals and/or angioedema only in the presence of more than one trigger (eg cold and exercise in patients with cold-induced cholinergic urticaria).

CSU was reported in 1.8% of ColdU patients.[6] In clinical practice, ColdU occurs in around 5% of CSU patients, with studies reporting up to 13% of CSU patients.[109] The pathophysiological links between ColdU and comorbid CSU as well as the interdependency of CIndUs are not understood (Table 1, Section 5).

6.1 | Clinical course

The average ColdU duration has been reported to be approximately 6 years (Supplementary materials, Table S1),[6,35,40,41,43,48,49,51,53] but the disease may persist for 20 years or longer.[6,28,34,35,46] Clinical predictors for ColdU of long duration include early onset, severe disease, and higher CTTs.[35] Overall, the natural history of ColdU, including the progression rate from acute to chronic ColdU, the kinetics, the drivers of spontaneous remission and the relapse rate, are ill characterized.

Individual CSTTs were suggested as a clinical predictor for severe ColdU.[11,35,41] Typically, patients develop symptoms within 1-5 minutes after cold exposure.[63] In a study by Wanderer and colleagues, type III reactions were more frequent in patients with a rapid onset of symptoms (≤3 minutes) after CST.[11] Likewise, in the study by Deza and co-workers, patients with type III reactions had shorter CSTTs than those with type I and II reactions.[35] There is a need for further research on prognostic biomarkers for persistent, life-threatening or fatal ColdU (Table 1, Section 6).

7 | DIAGNOSTIC ALGORITHM

The diagnosis of ColdU relies on the patient's history and CST, which should be carried out with an ice cube and/or Temp*Test*.[1,103] Routine testing with cold packs or cold water baths is not recommended. Second-generation H_1-antihistamines (sgAH) and systemic

glucocorticoids should be discontinued at least 3 and 7 days prior to testing, respectively.[1] A melting ice cube in a thin plastic bag or non-latex medical glove is applied to the forearm for 5 minutes (1A), followed by the test reading 10 minutes after the end of cold stimulation (Figure 1B).[1] A positive result is demonstrated by whealing (Figure 1B) with or without itching in the contact area with ice.[1] Siebenhaar and co-workers estimated the sensitivity of the ice cube test at 83% and the specificity at 100%.[7] In the study by Holm and colleagues, the sensitivity of an ice cube test was 53% and the specificity 97%.[110] This discrepancy is likely to reflect the variation in cold sensitivity, the accuracy and the certainty of patient's clinical history and the frequency of atypical ColdUs in the studied patient populations. Ice cube testing has the advantage of measuring the CSTT and the limitation of not allowing CTT assessments.

In clinical practice, threshold testing, using Temp*Test* methodology, offers the advantage of a standardized CST,[1,7,111,112] providing objective, reproducible and validated results:

- To assess ColdU activity[37];
- To obtain evidence for spontaneous remission[112];
- To identify ColdU patients with a high risk of ColdA,[35] who are likely to benefit from an early prescription of epinephrine autoinjectors, higher doses of sgAH and treatment with biologics, although treatment responses currently cannot be predicted;
- To guide cold avoidance in patients' daily lives and work[45];
- To monitor therapeutic interventions (Supplementary materials, Table S2)[36,43-45,47,66,113,114];
- To develop personalized treatment plans for ColdU patients.[115]

Threshold testing includes CTT and CSTT assessments (Section 5). CTT testing is performed with the standardized Temp*Test* device, which consists of a single U-shaped piezoelectric element that generates a temperature range from 4°C to 44°C. The Temp*Test* technology is based on the Peltier effect, comprising heating or cooling of plastic embedded thermoelectric elements according to the polarity and voltage of an electric current passing through 2 semiconductors.[7,111] Temp*Test* testing allows measurements of CTTs with an accuracy of ±1°C.[9] The validation of the grading of CTTs for clinical use warrants further research (Table 1, Section 7).[45]

Importantly, CTT testing determines the critical skin temperature rather than the critical exposure temperature, for example air or water temperature.[45] These are not the same, as thermoregulatory mechanisms allow the skin to counteract the adoption of environmental temperatures.[116,117] The thermoregulatory responses to cold exposures in ColdU[118] are poorly understood and are of great clinical interest (Table 1, Section 7).

ColdU patients with a negative CST need further evaluation. Firstly, in some patients, a longer provocation time (up to 20 minutes) may be appropriate (Table 2).[1,6] Submersion of one hand as an alternative to an ice cube test was first described as a research tool,[61] but can also be used for diagnosis. With caution, the immersion of one forearm in water of 5-10°C is carried out for up to 15 minutes.[1] Secondly, other tests for atypical ColdUs are recommended (Table 2). In difficult cases, cold challenge conditions should be adapted to mimic the real situations that induce patients' symptoms.[1] Additionally, testing with other physical stimuli can be performed when there is a discrepancy between the clinical history and the results of challenge tests in physical urticarias.[119] Finally, in ColdU patients with a negative CST, an interdependency between cold and other physical triggers should be considered.

In a prospective National Institute of Health (NIH)–based study, 25% ColdU patients had a negative CST.[119] Deza and co-workers reported that 50% of patients with an early onset (≤18 years old) of ColdU had a negative ice cube test.[35] The pathophysiology underlying a negative CST in atypical ColdU represents an enigma (Table 1, Section 7), which perhaps can be resolved with more sensitive techniques (infrared thermography or 3-dimensional volumetry imaging).[47]

8 | LABORATORY WORK-UP IN COLDU PATIENTS

According to the EAACI/GA^{2}LEN/EDF/UNEV guidelines for urticaria, the laboratory work-up for ColdU patients includes a differential blood count and erythrocyte sedimentation rate or C-reactive protein (CRP).[1,120] Additional diagnostic work-up, including a search for underlying infections (Table 3), should only be done if indicated by the patient's history or required for the differential diagnosis. However, there is no guidance on the clinical relevance of positive viral serology or cryoglobulins in ColdU. In most studies, cryoglobulins were detected in less than 1% of ColdU patients[6,11,121-123] (Supplementary materials, Table S1), and their pathogenic role in ColdU is unknown. Clearly, further research into the role of infections or cryoglobulins in ColdU is needed (Table 1, Section 8).

9 | THE DIFFERENTIAL DIAGNOSES OF COLDU

ColdU is not the only disease that presents with cold-associated whealing (Table 6). The differential diagnoses of ColdU include cryopyrin-associated periodic syndromes (CAPS),[124,125] phospholipase Cγ2-associated deficiency and immune dysregulation (PLAID)[126] and rarely CryoVas, which require different diagnostic approaches. The differential diagnostic work-up of cold-induced whealing should incorporate genetic testing in neonatal cases and skin histology if CryoVas is suspected. In the future, systems biology approaches and machine learning algorithms may improve the differential diagnostic work-up in patients with cold-induced whealing (Table 1, Section 9).

9.1 | Autoinflammatory diseases need to be ruled out in patients with cold-induced whealing

Neonatal-onset cold-induced whealing is highly suggestive of CAPS.[124,125] Cold-induced episodes of urticaria-like rash may be

present in all CAPS subtypes,[127] but typically occur in familial cold autoinflammatory syndrome (FCAS).[125] In FCAS, the genetic defect can be heterozygous germline or somatic gain-of-function mutations in the *NLRP3* gene encoding nucleotide oligomerization domain (NOD)-, LRR- and pyrin domain-containing protein 3 (NLRP3), also known as cryopyrin (Table 6).[128] In contrast to CAPS, ColdU rarely occurs in infancy, is not associated with fever or arthralgia,[125] and is not related to germline or post-zygotic variants of *NLRP3*, *NLRP12*, *NLRC4* and *PLCG2* genes as demonstrated by next generation sequencing.[129] Unlike the typical itchy wheals in ColdU, CAPS patients show a wide spectrum of skin lesions including flat, non-itchy or minimally itchy wheals and erythematous patches.[130] The timing of cold-induced lesions is different in ColdU and CAPS (Table 6). The wheals in ColdU appear immediately after cold exposure and remit without sequelae, whereas cold-induced cutaneous signs and symptoms in CAPS usually take 1-2 hours to develop and are often followed by fever and arthralgia 4-6 hours later.[130,131] Importantly, cold-induced skin lesions in CAPS patients cannot be induced by CSTs and require generalized cold exposure to occur. In patients with a negative CST, atypical ColdU is a differential diagnosis of CAPS. Characteristic lesions in cold-induced cholinergic urticaria or cold-dependent dermographism can help differentiate atypical ColdU from CAPS. Additionally, atypical ColdUs are not associated with fever and arthralgia, and a cold room provocation can help to establish the diagnosis.[125,132]

In clinical practice, the diagnosis of FACS is often delayed and relies on molecular genetic testing for the mutations in the coding part of the *CIAS1* gene (*NLRP3*) by direct sequencing in the specialized centres.[127,131,133] *CIAS1* mutations remain undetected in over 50% of patients.[127,131] The probability of positive genetic testing results can be enhanced by using clinical selection criteria: three or more recurrent bouts, disease onset < 20 years, elevated CRP, especially in patients with wheals and fever.[127]

The phenotypic expression of CAPS represents a clinical spectrum with overlapping features between different autoinflammatory syndromes.[134] The diagnostic model for all CAPS subtypes regardless of *NLRP3* mutation includes raised inflammatory biomarkers (CRP/serum amyloid A) plus ≥ two of six symptoms: urticarial-like rash, cold-triggered episodes, sensorineural hearing loss, musculoskeletal symptoms, chronic aseptic meningitis and skeletal abnormalities.[127] Prompt diagnosis is crucial for a rapid initiation of IL-1 blockade for treatment and prevention of AA amyloidosis, which is reported to develop in 2-4% of cases.[125,127]

Other mutations (*NLRP12*, *NLRC4*) were also linked to an early-onset cold-induced urticarial rash and an autoinflammatory phenotype.[135,136] Cold-induced urticarial rash can be a feature of a newly described FXII-associated cold autoinflammatory syndrome (FACAS) associated with a substitution mutation in the *F12* gene encoding the human coagulation factor XII.[137] In FACAS, cold-induced whealing begins in infancy, occurs within 10-30 minutes after whole-body exposure to ambient temperatures below 15-20°C, and may last for several hours. FACAS is associated with a negative ice cube test or cold water bath.[137]

Rarely, neonatal cold-induced whealing can be a clinical characteristic of PLAID, presenting with a hereditary complex of cold-induced wheals, antibody deficiency, susceptibility to infections and autoimmunity due to genomic deletions in *PLCG2* gene, encoding phospholipase $C\gamma_2$ – a signalling messenger in B cells, natural killer cells and MCs.[126] These patients present with a negative ice cube test but react to skin testing for evaporative cooling by using droplets of ethanol or air-blown water.[132]

9.2 | Cryoglobulinemic vasculitis needs to be ruled out in patients with cold-induced whealing

Cold-induced skin inflammatory responses may occur in CryoVas (Table 6), which can be associated with infections (hepatitis C, human immunodeficiency virus (HIV), etc), autoimmune (Sjögren's syndrome, systemic lupus erythematosus, etc) and lymphoproliferative (multiple myeloma, chronic lymphocytic leukaemia, B-cell non-Hodgkin's lymphoma, etc) disorders,[92-94] or mixed cryoglobulinemia.[138-141] Skin lesions in CryoVas are predominantly purpura and ulcers, and rarely wheals.[142,143] The diagnosis is established based on clinical features, laboratory findings (cryoglobulinemia and rheumatoid factor due to rheumatoid factor activity of cryoglobulins[144]), and renal or skin histology suggestive of leucocytoclastic vasculitis with the deposition of cryoglobulin immune complexes.[92,140,145] The early diagnosis of CryoVas is important for prompt treatment directed towards aetiology, the detection of systemic manifestations and the prevention of life-threatening complications.[139,141,145,146]

9.3 | Other diseases that need to be ruled out in patients with cold-induced whealing

Mastocytosis, cold panniculitis and chilblain lupus erythematosus should be included in the differential diagnosis of ColdU. Patients with mastocytosis may present with whealing caused by physical triggers including cold[147] and should be evaluated as per the diagnostic algorithms for children and adults.[148] In cold panniculitis, local painful deep swelling may appear 6-72 hours after cold contact, with post-resolution hyperpigmentation.[10] Chilblain lupus erythematosus is a rare variant of chronic cutaneous lupus erythematosus,[149] which is characterized by cold-induced lesions in acral areas. Chilblain lupus erythematosus is diagnosed using the Mayo diagnostic criteria[150] and should be differentiated from idiopathic perniosis, lupus pernio associated with sarcoidosis[151] or chilblain-like lesions in coronavirus disease 2019 (COVID-19).[152]

10 | MANAGEMENT

The management of ColdU should provide patients with guidance on trigger avoidance or mitigation as well as with treatments that prevent signs and symptoms and help to control them, when they

TABLE 6 Differential diagnosis of cold-induced conditions

	Cold urticaria (ColdU)	Familial cold autoinflammatory syndrome (FCAS)	Cryoglobulinemic vasculitis (CryoVas)
Prevalence	0.05% in the population	Appr. 1:1,000,000	<5 cases per 10,000 Approximately 35-70% of patients with hepatitis C
Disease onset	Mostly 2nd to 4th decades of life	After birth/infancy	5th to 7th decades of life
Causes and clinical associations	1. Infections 2. Autoimmune diseases 3. Lymphoproliferative diseases 4. Drugs 5. Foods 6. Insect stings	The mutation in the *CIAS1* gene in the chromosome 1q44	Viral hepatitis C HIV infection, etc
Disease trigger	Direct skin contact with cold air, objects, liquids	Generalized cold exposure Stress Infections	Ambient temperature less than 37°C
The onset and duration of symptoms	1-5 min after the cold exposure, resolve within one hour or longer.	1-2 h after cold exposure, resolution within 12-48 h	May persist for over 24 h, marked hyperpigmentation
Predisposition	Female predominance	Autosomal dominant mode of inheritance	Female predominance
Anaphylaxis	5%-50% of patients	–	–
Skin lesions	Wheals/angioedema	Generalized wheals or erythematous papules and plaques	Purpura, ulcers, livedo, rarely wheals
Other symptoms	Headache, fever, fatigue Nausea, abdominal pain, diarrhoea Tachycardia, shortness of breath Hypotension, shock Uterine contractions Disorientation, vertigo	Musculoskeletal involvement, chills/fever, headache, fatigue, Conjunctivitis Gastrointestinal involvement, Macrophage activation syndrome in severe phenotypes Amyloidosis	Arthralgia, myalgia Weakness, fever Polyneuropathy, rarely mononeuropathy Glomerulonephritis, Raynaud's phenomenon Congestive heart failure Lymphadenopathy Liver abnormalities
Diagnostic tests	Ice cube test Temp*Test* test	Mutation analysis (*CIAS1* gene)	Cryoglobulins Skin / kidney biopsy Rheumatoid factor[144]
Cryoglobulins/cryofibrinogen	<1% of patients	Not defined	55-90% of patients
Skin histology	Mast cell degranulation, perivascular cellular infiltration (lymphocytes, neutrophils and eosinophils)	Dermal oedema, perivascular infiltration (mostly neutrophils)	Leukocytoclastic vasculitis
Comorbidity	Atopic diseases Chronic spontaneous urticaria Chronic inducible urticarias	–	Hepatitis C or B Autoimmune diseases B-cell lymphoproliferative diseases, etc

occur.[1,120] Trigger thresholds should be measured in all patients, before the start of a new treatment and during the course of the treatment, to determine its efficacy.[59]

10.1 | The importance of avoiding and mitigating triggers

Cold avoidance measures are of primary importance in ColdU[1,120,132] and include lifestyle modifications and normothermic conditions during surgery or labour (Table 7).[153-155] However, the effectiveness of cold avoidance measures is limited, and their effects including those on patient's QoL warrant further research (Table 1, Section 10).

10.2 | Treatment of ColdU

According to the EAACI/GA^{2}LEN/EDF/UNEV guidelines for urticaria, sgAH in licensed and high doses are the first- and second-line ColdU treatment, respectively.[1,120] Mechanistically, sgAH exert their biological effects by stabilizing the histamine H1 receptor (H1R) in its inactive state (inverse agonism). The meta-analysis of 9 randomized

TABLE 7 Recommendations to the patients with ColdU

Lifestyle modifications for the patients with ColdU	
Be careful visiting places with low ambient temperature:	Supermarkets (departments with refrigeration)
	Warehouses, cellars
	Rooms with active use of air conditioners, especially in the warm season (shops, public transport, offices)
	Skating rinks, ice arenas
	Cosmetology, dental and treatment rooms
Take precautions when travelling to:	Caves
	Mountains
	Mountain rivers and lakes
Be cautious while doing household activities:	Defrosting the refrigerator
	Window cleaning
Avoid cosmetic procedures involving an exposure to cold:	Cryorejuvenating therapy (cryocapsule, etc)
Avoid:	Ice cream
	Ice
	Fruits and vegetables without pre-warming when stored in the refrigerator
	Cold foods, drinks (temperature should not be below 24°C)
Refrain from water and winter sports:	Swimming
	Diving
	Water polo
	Hockey
	Figure skating
	Skiing, snowboarding
	Curling
High-risk occupations include:	Scuba divers
	Butchers, workers of warehouses and departments of frozen products
	Sailors, fishermen, cooks
	Polar explorers
	Climbers
	Pathologists, surgeons, anaesthesiologists
Recommendations for the perioperative management of ColdU patients	
Air temperature control in the operating room	
Monitoring the patient's body temperature, blood pressure, heart rate, breathing rate. Should systemic reactions occur, use epinephrine and glucocorticoids.	
Use of premedication (glucocorticoids, antihistamines)	
Pre-warming of solutions for parenteral use	
Warming the patient during surgery (blankets, heaters)	
Avoid using chloroethyl, treating large skin surfaces with alcohol and antiseptic solutions, do not use ice and cooling elements.	

controlled studies (RCTs) proved sgAH effective in ColdU.[156] The effectiveness of updosing of sgAH in ColdU, which is currently off-label, was demonstrated in two systematic reviews.[156,157] In the meta-analysis of 4 RCTs, there was a significant reduction in CTTs in ColdU patients while treated with high doses of sgAH (bilastine,[44] desloratadine,[47] and rupatadine[36,114]) compared to licensed doses or placebo.[156] Temp*Test* provocation testing is a useful tool for an objective measurement of sgAH efficacy in ColdU (Supplementary materials, Table S2). Bilastine updosing to 80 mg/day significantly reduced the release of histamine, IL-6 and IL-8 after a CST according to microdialysis data.[44]

Given the individual responses to sgAH,[38,45] the choice of sgAH and the daily dose can be personalized.[115] Up to 30% of ColdU patients achieve a complete protection from cold-induced whealing when treated with high-dose sgAH.[45] However, sgAH therapy is unlikely to prevent ColdA in ColdU patients upon an extensive cold exposure. Further studies are required to optimize the protection from cold exposures in ColdU patients with high risk of ColdA.

Notably, about 20% of ColdU patients did not show any reduction in CTT even when treated with high-dose sgAH.[45] The mechanisms underlying sgAH resistance in ColdU are largely unknown. It is unclear whether the treatment failure with sgAH may be due to certain polymorphisms in histamine receptors or histamine-metabolizing enzymes, an involvement of other histamine receptor subtypes such as histamine H2 (H2R) or H4 (H4R) receptors, or an involvement of receptors other than histamine receptors. Shedding light on these mechanisms may require combination treatments. Specifically, targeting both H1R and H4R might bring added benefit over monotherapy and may be a compelling approach in ColdU.

Patients, who fail to respond to a sgAH, may benefit from off-label therapy with anti-IgE monoclonal antibody, omalizumab, which targets circulating IgE and affects MC/basophil function.[1] The efficacy of omalizumab in ColdU patients was demonstrated by a meta-analysis, including one randomized placebo-controlled study, 4 sizeable case series (≥5 patients) and 6 case reports (<5 patients), and totalling to 52 omalizumab- and 12 placebo-treated patients.[158] In the placebo-controlled RCT, the clinical effect of omalizumab 150 mg and 300 mg was observed as early as week 4.[63] Omalizumab dosing can be individualized in the range 150-600 mg/month.[63,158]

Little is known about the treatment strategy for omalizumab-refractory patients. There is scarce data on ciclosporin efficacy in ColdU.[159] Alternative treatment options include tricyclic antidepressants (doxepin) and immunosuppressive drugs (azathioprine, mycophenolate mofetil).[1] However, the use of these medications is limited by their potential toxicity and a low level of evidence. ColdU patients may respond to a therapy with cinnarizine,[50] and antibiotics.[10,39,160] Biological therapeutics licensed for other conditions (anakinra, etanercept, reslizumab and dupilumab) appear to have efficacy in ColdU based on case reports.[76,161-163] Topical Syk inhibitor (theclinicaltrials.gov identifier – NCT02424799) and rilonacept (an interleukin 1 blocker; theclinicaltrials.gov identifier – NCT02171416) are being developed for ColdU.

Current guidelines recommend the prescription of epinephrine autoinjector for patients at risk of systemic reactions.[132] Clearly, there is an uncertainty on the prescription criteria for epinephrine autoinjector in ColdU (Table 1, Section 10). Although ColdU patients with a positive CSTT of less than or equal to 3 minutes or with oropharyngeal angioedema following an intake of cold foods or beverages were described to be at increased risk of ColdA,[11,41] in clinical practice ColdA can occur in ColdU patients with a CSTT of more than 3 minutes or a negative CST.[11,42,106] A recent survey of doctors demonstrated that 48% of study respondents prescribe epinephrine autoinjectors to less than 10% of their ColdU patients,[106] although a rate of systemic reactions in ColdU was estimated at 26%-70% (Supplementary materials, Table S1). These data suggest a discrepancy in the rate for systemic reactions in ColdU in the literature and the real clinical practice highlighting the clinical need for a guidance on epinephrine prescription in ColdU.[106] Besides, there is no available data on the epinephrine efficacy or the optimal number of epinephrine injections in patients with ColdA. It remains unclear whether other medications could be used in addition to epinephrine in ColdA (Table 1, Section 10). These questions need to be addressed in real-life studies.

Cold desensitization is the induction and maintenance of cold tolerance through continued cold exposure.[164] Its mechanism is poorly understood. Desensitized patients have little or no HR to cold challenge but unaltered response to codeine.[46] Cold desensitization protocols are not routinely used because of the risk of ColdA, patient noncompliance with daily cold showers, and a rapid and marked loss of effect in the absence of regular cold exposure.[9,45,132]

Future studies aimed at the predictive biomarkers in ColdU are awaited, since predictive biomarkers for various treatments in ColdU are currently lacking (Table 1, Section 10).[115]

11 | CONCLUSIONS AND OUTLOOK

In conclusion, ColdU remains a fascinating area of research, representing an optimal experimental model for urticarial conditions to answer mechanistic and clinical questions (Figure 2). An international multi-centre observational prospective study COLD-CE, supported by the GA^{2}LEN UCARE network, is being conducted with an aim to globally improve the understanding of ColdU and ColdA. The pathophysiology of ColdU and ColdA is a research priority. Oropharyngeal angioedema and/or ColdA in ColdU prompt further RCTs of innovative agents. In the future, the use of genomic, postgenomic and machine learning approaches are the next frontier in the ColdU research leading to novel therapeutic targets.[165]

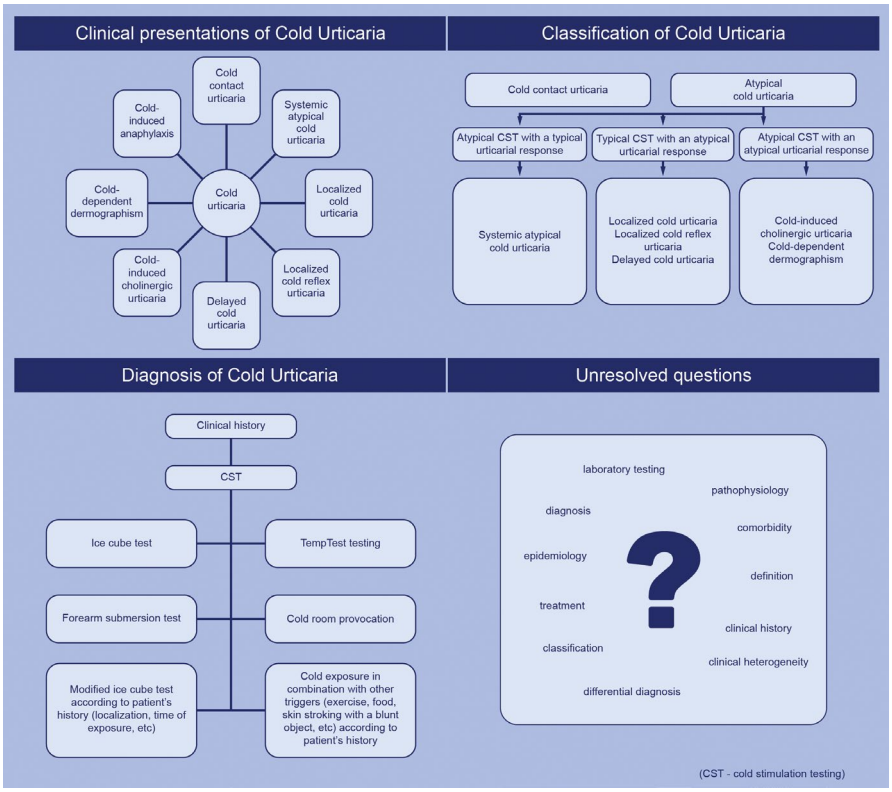

FIGURE 2 Cold urticaria is classified into cold contact urticaria and atypical cold urticaria based on clinical presentations and response to cold stimulation testing (CST). In cold urticaria patients with negative ice cube and Temp*Test* testing, additional CST should be used to diagnose the variants of atypical cold urticaria including systemic atypical cold urticaria, localized cold urticaria, localized cold reflex urticaria, delayed cold urticaria, cold-induced cholinergic urticaria and cold-dependent dermographism. The mechanisms underlying clinical heterogeneity of cold urticaria and several aspects of its management provide important avenues for further research.

ACKNOWLEDGEMENTS

This report benefitted from the support of the GA²LEN urticaria centres of reference and excellence (UCARE) network (www.ga2len-ucare.com).

CONFLICT OF INTEREST

NM participates as an investigator in a clinical trial sponsored by Novartis. EB received honoraria for educational lectures from Novartis and Sanofi and research funding from GSK. DF received honoraria from Novartis, Shire, Behring CSL and Sanofi. MB has been a speaker and an advisor for Novartis. KK received honoraria for educational lectures from Menarini and Novartis. RM received honoraria from Novartis. SFT has been a speaker, served on advisory boards and received research support from AbbVie, Celgene, Eli Lilly, Janssen, LEO Pharma, Novartis, Pfizer, Roche, Sanofi and UCB. MM is or recently was a speaker and/or an advisor for and/or has received research funding from Allakos, Aralez, AstraZeneca, FAES, Genentech, Lilly, Menarini, Novartis, Moxie, MSD, Roche, Sanofi, UCB and Uriach. MK and DTM declare no conflict of interests.

AUTHOR CONTRIBUTION

All authors contributed equally to the manuscript. COLD-CE (comprehensive evaluation of cold urticaria) is a project of the GA²LEN urticaria centres of reference and excellence (UCARE) network (www.ga2len-ucare.com).

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SUPPORTING INFORMATION

Additional supporting information may be found online in the Supporting Information section.

How to cite this article: Maltseva N, Borzova E, Fomina D, et al. Cold urticaria – What we know and what we do not know. *Allergy*. 2021;76:1077–1094. https://doi.org/10.1111/all.14674