Current Treatment Options in Allergy (2024) 11:167–175
https://doi.org/10.1007/s40521-024-00366-9

REVIEW

Risk of Anaphylaxis Associated with Cold Urticaria

Mojca Bizjak[1,2] · **Krzysztof Rutkowski**[3] · **Riccardo Asero**[4]

Accepted: 6 June 2024 / Published online: 20 June 2024

Abstract

Purpose of review Cold-induced anaphylaxis (ColdA) is a poorly understood form of anaphylaxis that occurs in patients with cold urticaria (ColdU). This comprehensive review aims to deepen the understanding of ColdA. It emphasizes the identification of high-risk ColdU patients susceptible to ColdA and provides recommendations for their effective management.

Recent findings Recent studies, including the large international COLD-CE study, have identified clinical features of ColdU patients associated with increased ColdA risk. These individuals can now be recognized through routine clinical assessments. Key diagnostic indicators for assessing ColdU and the risk of ColdA include oropharyngeal/laryngeal symptoms and positive standard local cold provocation tests. ColdA has been defined as acute cold-induced involvement of the skin and/or visible mucosal tissue accompanied by cardiovascular manifestations, difficulty breathing, or gastrointestinal symptoms, but a universally accepted definition is lacking. Additionally, ColdA has recently been recognized as an indication for prescribing adrenaline (epinephrine) autoinjectors, marking a significant advancement in disease management.

Summary ColdA is a major and potentially life-threatening concern for a subset of ColdU patients. Early recognition of high-risk patients, coupled with education and preparedness of both patients and healthcare providers, is crucial for effectively managing this challenging condition. Further research is needed to expand understanding of the underlying pathophysiological mechanisms of ColdA, identify potential cofactors influencing ColdA, and improve disease-management strategies.

Keywords Adrenaline (epinephrine) · Autoinjector · Cold-induced anaphylaxis · Cold urticaria · Management · Risk factors

Abbreviations

AAI(s)	Adrenaline (epinephrine) autoinjector(s)
CIndU	Chronic inducible urticaria
CMCD(s)	Clonal mast cell disorder(s)
ColdA	Cold-induced anaphylaxis
COLD-CE	Comprehensive evaluation of cold urticaria and other cold-induced reactions, a study within the GA^{2}LEN UCARE network
ColdU	Cold urticaria
ColdU^A	Atypical cold urticaria
ColdU^T	Typical cold urticaria
CSTT	Critical stimulation time threshold
CTT	Critical temperature threshold
HVA	*Hymenoptera* venom-triggered anaphylaxis
IgE	Immunoglobulin E
LCP	Local cold provocation
MC(s)	Mast cell(s)

Introduction

Anaphylaxis is the most severe immediate systemic allergic reaction, usually rapid in onset and sometimes fatal [1]. It generally involves at least two organ systems, including the skin/visible mucosal tissue, cardiovascular, respiratory, or gastrointestinal system. Possible symptoms and clinical signs of anaphylaxis are listed in Table 1 [2–5, 6••]. Immediate administration of adrenaline (epinephrine) is crucial [2], but often underused [3, 7]. Cold-induced anaphylaxis (ColdA) represents a poorly researched form of anaphylaxis in patients with cold urticaria (ColdU). ColdU, a subset of

✉ Mojca Bizjak
mojca.bizjak@klinika-golnik.si

1 Faculty of Medicine, University of Maribor, Maribor, Slovenia

2 Division of Allergy, University Clinic of Respiratory and Allergic Diseases Golnik, Golnik 36, 4204 Golnik, Slovenia

3 Department of Allergy, Guy's and St Thomas' Hospital and Urticaria Clinic, St John's Institute of Dermatology, London, UK

4 Clinica San Carlo, Ambulatorio Di Allergologia, Milan, Paderno Dugnano, Italy

Table 1 Possible symptoms and clinical signs of anaphylaxis [2–5, 6••]

System	Symptoms and signs
Skin, visible mucosal tissue	Flushing Pruritus Wheals Angioedema
Cardiovascular system	Dizziness, lightheadedness, confusion (due to decreased blood flow to the brain) Hypotonia, weakness (reduced muscle tone with weak muscle strength) Collapse (abrupt loss of postural tone leading to falling or lying down involuntarily) Syncope (temporary loss of consciousness due to decreased blood flow to the brain) Tachycardia Blood pressure < 90/60 mmHg
Respiratory system	Dysphagia (difficulty swallowing) Dysphonia (hoarseness due to laryngeal edema) Dyspnea (subjective feeling of breathing discomfort; e.g., breathlesness, tightness in the chest, a sense of suffocation) Wheeze (high-pitched whistling sound during breathing, particularly when exhaling; a sign of bronchoconstriction) Stridor (distinct high-pitched sound predominantly heard when inhaling; a sign of blockage at or above the level of vocal cords) Sneezing, cough Chest pain
Gastrointestinal system	Crampy abdominal pain Vomiting Diarrhea

chronic inducible urticaria (CIndU), has an estimated annual incidence of 0.05% in Europe [8] and is characterized by the development of wheals and/or angioedema upon exposure to cold stimuli followed by rewarming [9–11, 12••, 13]. The precise fatality rate associated with ColdA is unknown [9, 12••, 14, 15•]. ColdA remains poorly understood due to the absence of a universally accepted definition and limited knowledge of its pathomechanism. This manuscript aims to review: (a) recent research findings, including those from the large international, cross-sectional COLD-CE study (i.e., comprehensive evaluation of ColdU and other cold-induced reactions, a study within the GA^{2}LEN UCARE network) [12••, 16••, 17], and (b) effective management strategies. Additionally, we discuss the potential involvement of mast cells (MCs) and basophils, along with the role of immunoglobulin E (IgE) to autoallergens, in the pathogenesis of ColdA.

Classification of ColdU: distinguishing typical and atypical forms through provocation

Standard methods of local cold provocation (LCP) involve the use of an ice cube melting in a plastic bag or nonlatex glove and/or a thermoelectric device, the Temp*Test*® with a 4 – 44 °C gradient, on the volar forearm [18]. ColdU is clinically categorized into two forms: typical ColdU (ColdU^T), characterized by immediate whealing in the area of LCP, and atypical ColdU (ColdU^A), with either negative LCP tests or atypical responses, such as delayed whealing. For ColdU^A, specific provocation methods tailored to individual patient histories are often necessary to elicit whealing [9, 18, 19]. In ColdU^T, provocation thresholds should be determined if possible [18]. The critical stimulation time threshold (CSTT) is the minimum contact time (30 s to 5 min) with an ice cube that induces a wheal, and the critical temperature threshold (CTT) is the highest temperature (4 – 37 °C) at which a wheal is induced by Temp*Test*® [12••, 18]. The prevalence of ColdU^T in ColdU studies shows significant variability (59 – 100%), indicating potential differences across various populations and settings [11, 12••, 20–30]. While ColdU is predominantly an acquired condition, rare hereditary forms have been identified [31]. The associated risk of ColdA in these hereditary forms remains unknown.

Variability in the definition and reported prevalence of ColdA

The definition of ColdA lacks consensus. In the COLD-CE study, ColdA was diagnosed in 37% (151/412) of patients with ColdU^T. This study defined ColdA as an acute cold-induced involvement of the skin and/or visible mucosal tissue accompanied by at least one of the following: cardiovascular manifestations (i.e., hypotension [RR < 90/60 mmHg] or signs or symptoms suggestive of hypotension [loss of consciousness, dizziness, sensation of fainting, weakness]), breathlessness, or gastrointestinal symptoms [12••, 16••]. Previous smaller-scale studies reported systemic reactions,

based on variable definitions, in 4 – 51% of ColdU patients [11, 20–30, 32–36], as indicated in Table 2. There are significant challenges in determining the prevalence of ColdA due to its patient-reported nature (often not formally documented/coded by healthcare providers) and the influence of trigger avoidance. It should also be emphasized that the prevalence of ColdA derives exclusively from individual clinical history as, for ethical reasons, nobody would systematically expose patients with ColdU to a cold environment (e.g., bath, shower, room) to establish whether they develop an anaphylactic reaction. Environmental factors such as geographical characteristics also very likely play a role in the development of ColdU/ColdA [37]. A systematic review and meta-analysis identified a 21% prevalence of ColdA, defined as a systemic reaction involving two organ systems and/or hypotension triggered by cold exposure among ColdU cases [15•]. Additionally, a few studies provided data on individual systemic reactions (Table 2) [11, 12••, 22–24, 38]. Comparative studies of ColdA prevalence in $ColdU^{T}$ versus $ColdU^{A}$ are limited. Two studies revealed a higher incidence of ColdA in $ColdU^{T}$ patients (Table 2) [26, 34].

Underrepresentation of ColdA in anaphylaxis publications

Ring and Behrendt (1999) reported that cold can act as an elicitor of 'pseudoallergic (anaphylactoid) hypersensitivity reactions' [4]. Subsequently, Kemp and Lockey (2002) listed cold temperatures as a cause of 'IgE-independent (anaphylactoid) reactions' [39], and Simons et al. (2007) recognized cold as a non-immunologic trigger or a co-trigger of anaphylaxis [40]. The 2011 World Allergy Organization guidelines also mentioned cold as a non-immunologic trigger of anaphylaxis [5]. Williams and Sharma (2015) further identified cold as one of the non-immunologic triggers of anaphylaxis due to the direct activation of MCs and basophils [41]. In a clinical context, Sala-Cunill et al. (2013) found only one ColdA patient in a cohort of 102 anaphylaxis cases [42], and Yeğit et al. (2023) reported just one ColdA patient among 271 anaphylaxis cases [43]. However, in 2023, the Joint Task Force on Practice Parameters recognized ColdA as a form of anaphylaxis associated with physical stimuli and recommended that patients with ColdU may require adrenaline (epinephrine) autoinjectors (AAIs) [6••]. This represents the first official recognition of ColdA as an indication for AAIs.

Systemic cold exposure as the primary trigger of ColdA

The same type of cold exposure does not uniformly result in the same severity of ColdU in all patients [12••, 21, 22, 24, 28, 44, 45]. The primary exogenous risk factors for ColdA appear to be the extent of skin surface area exposed, the temperature, and the duration of the exposure. This correlation likely explains why complete water immersion is the most frequently reported trigger of ColdA [12••, 16••, 20, 22, 24, 26, 28, 33, 38]. This relationship suggests a dose-dependency in ColdA [9]. Other documented triggers of ColdA include exposure to cold air [12••, 16••, 22, 26, 33, 38], localized contact with cold water [25, 33], limited contact with cold solid surfaces [26], cold provocation in the clinical setting [13], consumption of cold food or drinks [11, 26, 33, 46], and exposure to intravenous or irrigation fluids [33, 47–49]. Currently, no cofactors are known that may influence the severity of ColdA.

Key diagnostic indicators for assessing the risk of ColdA

It is essential to take a detailed patient history and perform standard LCP tests in all patients reporting symptoms of ColdU or ColdA. Previous studies identified the following 'endogenous' clinical characteristics of patients with ColdU who have previously experienced ColdA episodes: (a) prolonged duration of ColdU [12••, 26]; (b) cold-induced oropharyngeal/laryngeal signs or symptoms, such as swollen tongue and uvula, difficulty swallowing (dysphagia), or voice changes (dysphonia) [12••, 28]); (c) cold-induced generalized wheals, angioedema, or itchy earlobes [12••]; (d) positive standard LCP, indicating $ColdU^{T}$ [26, 33, 34]; (e) shorter CSTTs [12••, 26, 28, 29] and higher CTTs [26] in LCP; (f) larger wheal diameters in LCP [12••]; (g) pseudopodial whealing in LCP [12••]; and (h) a history of systemic reactions to *Hymenoptera* stings [12••]. On the other hand, the presence of concomitant chronic spontaneous urticaria was associated with a decreased risk of ColdA in patients with $ColdU^{T}$ [12••].

Pathophysiology of ColdA

The pathomechanism of 'typical' IgE mediated anaphylaxis has been extensively studied. It is known to involve various mediators released from activated MCs and basophils such as histamine, platelet-activating factor, enzymes, cysteinyl leukotrienes, and anaphylatoxins [50, 51]. While ColdU is understood as a MC-driven disease [10, 52–55], with heterogeneous activating signals [10, 56], the pathophysiology of ColdA remains largely unexplored [57]. We hypothesize that ColdA also predominantly involves MC and basophil activation.

Table 2 Cold-induced systemic reactions and their triggers: a summary of studies (1985 – 2023)

Study	Year	Age group	Definition of systemic reactions (SysR)	Frequency of SysR % (n/N)	Triggers of SysR	Cardiovascular % (n/N)	Respiratory % (n/N)	Gastrointestinal % (n/N)
Tomei et al. [38]	2023	P	Acute cold-induced involvement of the skin and/or visible mucosal tissue, and at least one of the following: cardiovascular manifestations, difficulty breathing, or gastrointestinal symptoms	100% (21/21)	CWI, air	86% (18/21)	10% (2/21)	38% (8/21)
Bizjak et al. [12••]	2022	P/A	Acute cold-induced involvement of the skin and/or visible mucosal tissue and at least one of the following: cardiovascular manifestations (hypotension or signs/symptoms suggestive of hypotension [loss of consciousness, dizziness, weakness]), difficulty breathing, or gastrointestinal symptoms	39% (145/372) ColdU^{T}	CWI, air	31% (116/372)	18% (57/309)	10% (39/372)
Bizjak et al. [11]	2021	A	Sudden cold-induced onset of at least two of the following: involvement of the skin and/or mucosal tissue, respiratory involvement, reduced BP or associated symptoms, or gastrointestinal symptoms	33% (12/36) ColdU	—	28% (10/36)	36% (13/36)	14% (5/36)
Ginter et al. [30]	2021	P/A	—	47% (23/49) ColdU	—	—	—	—
Paulino et al. [32]	2021	P/A	Respiratory and/or cardiovascular compromise	33% (17/52) ColdU	—	—	—	—
Yee et al. [33]	2019	P	Urticaria and/or angioedema associated with airway, respiratory and/or abdominal symptoms and/or cardiovascular or neurologic symptoms suggestive of hypotension including dizziness, lethargy, sensation fainting, disorientation or shock or symptoms of shock	19% (77/415) ColdU	CWI, air, localized water contact, food, drinks, IV or irrigation fluids	—	—	—
Deza et al. [34]	2019	P/A	Episodes suggestive of hypotension (dizziness, disorientation or shock) or respiratory distress (shortness of breath or wheezing)	24% (12/50) ColdU, 28% (10/36) ColdU^{T}, 14% (2/14) ColdU^{A}	—	—	—	—
Kulthanan et al. [25]	2019	A	One patient experienced generalized wheals, dyspnea and collapse	4% (1/27) ColdU^{T}	Localized water contact	—	—	—
Stepaniuk et al. [35]	2018	P/A	—	4% (2/50) ColdU	—	—	—	—

Table 2 (continued)

Study	Year	Age group	Definition of systemic reactions (SysR)	Frequency of SysR % (n/N)	Triggers of SysR	Cardiovascular % (n/N)	Respiratory % (n/N)	Gastrointestinal % (n/N)
Jain and Mullins [20]	2016	P/A	Respiratory symptoms of noisy or difficulty breathing (dyspnoea, bronchospasm/wheeze, cyanosis/hypoxia) and/or cardiovascular compromise (loss of consciousness or reported presyncope)	28% (28/99) ColdU	CWI	—	—	—
Deza et al. [26]	2016	—	Episodes suggestive of hypotension (dizziness, sensation of fainting, disorientation, or shock) or respiratory distress (shortness of breath or wheezing)	19% (14/74) ColdU, 25% (13/53) ColdU^{T}, 5% (1/21) ColdU^{A}	Water, air, solid surfaces, food	—	—	—
Azkur et al. [36]	2016	P	—	7% (1/15) ColdU	CWI	—	—	—
Siebenhaar et al. [27]	2009	A	Circulatory complaints/dizziness or difficulty swallowing/difficulty breathing	33% (10/30) ColdU^{T}	—	13% (4/30)	—	—
Katsarou-Katsari et al. [21]	2008	A	Generalized urticaria or angioedema associated with hypotension (dizziness, fainting, disorientation, shock)	29% (18/62) ColdU	—	—	—	—
Alangari et al. [22]	2004	P	Episodes suggestive of respiratory distress (such as wheezing or shortness of breath) or hypotension (dizziness, sensation of fainting, disorientation, or shock)	—	—	27% (8/30)	17% (5/30)	—
Mathelier-Fusade et al. [28]	1998	—	Hypotension, dizziness, and fainting fits	34% (12/35) ColdU^{T}	CWI	34% (12/35)	—	—
Wanderer et al. [29]	1986	—	Generalized urticaria and/or angioedema associated with episodes suggestive of hypotension (dizziness, sensation of fainting, disorientation, or shock)	38% (19/50) ColdU^{T}	—	—	—	—
Doeglas et al. [23]	1986	P/A	—	—	—	36% (14/39)	8% (3/39)	—
Neittaanmäki [24]	1985	P/A	—	—	—	7% (16/220)	14% (31/220)	2% (5/220)

A, adult; *BP,* blood pressure; *ColdU,* cold urticaria; *ColdU^{A}*, atypical cold urticaria; *ColdU^{T}*, typical cold urticaria; *CWI,* complete water immersion; *IV*, intravenous; —, not provided; *P,* pediatric; *SysR,* systemic reactions

Mature MCs are primarily located in tissues exposed to external pathogens such as the skin, airways, and gastrointestinal tract [58], and are situated around blood vessels and nerves [59, 60]. Unlike MCs, basophils are histamine-containing cells that circulate in the blood and play a central role in many types of allergic reactions [13]. A study by Juhlin and Shelley in 1961 revealed histamine release in two patients with ColdA, with distinctive cytologic changes in tissue MCs and blood basophils. They suggested that cutaneous signs result from histamine release by cold-sensitive MCs in the dermis, and systemic symptoms arise from histamine release by cold-sensitive basophils [13]. Passive serum transfer experiments suggest that IgE plays a role in the pathogenesis of ColdU [31, 61–65]. The hypothesis that cold exposure may trigger the formation of de novo autoallergens and subsequent IgE-mediated responses [9, 31, 66] diverges from traditional views of anaphylaxis but could be crucial in understanding ColdA. A case of a 12-year-old girl with ColdU/ColdA successfully treated with anti-IgE therapy also suggests IgE involvement [67]. TRPM8 (transient receptor potential cation channel subfamily M [melastatin] member 8) proteins, which form Ca^{2+}-conducting cation channels activated by menthol or cold, have also been proposed as mediators of MC activation in ColdU [68].

In cases of *Hymenoptera* venom-triggered anaphylaxis (HVA), testing for underlying clonal MC disorders (CMCDs) is a well-established practice [69–72]. Given that HVA was recognized as an independent risk factor for ColdA in the COLD-CE study [12••], further research is needed to determine whether patients with ColdA also need to be tested for CMCDs. Furthermore, a case of severe ColdU with the KIT D816V variant reported in 2021 [11] supports the hypothesis of a connection between ColdA and CMCD. Valent et al. reported 'cold temperature' as one of the factors that can provoke anaphylaxis in patients with mastocytosis, attributing it to a temperature effect on MCs [73]. Akin et al. emphasized that the presence of hypotension during anaphylaxis increases the likelihood of an underlying CMCD [74].

Immediate management strategies for high-risk patients

Patients at high risk for anaphylaxis require provision of AAIs [75]. The COLD-CE study highlighted that only a minority of ColdA patients received adrenaline during their anaphylaxis episode or were prescribed an AAI [16••]. Recommendations for prescribing AAIs vary: Yee et al. and Alangari et al. advised that all pediatric patients with $ColdU^T$ should have AAIs [22, 33], while Katsarou-Katsari et al. extended this recommendation to all adult patients with $ColdU^T$ [21]. However, this approach may lead to high costs and unnecessary lifestyle restrictions for mildly affected ColdU patients. We propose prescribing AAIs to: (a) all patients with a previous episode of ColdA, especially those with cardiovascular reactions; (b) individuals reporting cold-induced oropharyngeal/laryngeal signs or symptoms; and (c) patients deemed high-risk by physicians, based on other previously discussed clinical features. Furthermore, making AAIs accessible in public areas, particularly at beaches and swimming pools, would be advisable due to the potential for cold exposure in these settings.

It is also crucial to recognize the challenges in applying existing ColdA definitions to certain ColdU cases. For instance, respiratory symptoms in ColdU patients with asthma might be due to an exacerbation of asthma triggered by cold air, rather than ColdA. Gastrointestinal discomfort from cold food or drinks might reflect mucosal cooling rather than ColdA. Ingestion of cold foods or beverages can cause localized angioedema in the oropharyngeal/laryngeal tract, leading to upper airway obstruction, which may not be ColdA per se but a sign of direct, localized mucosal sensitivity to cold.

Educational points for long-term management of high-risk patients

Patients at high risk of ColdA require not only comprehensive education but also regular medical follow-ups. The estimated duration of ColdU ranges from 4.8 to 7.9 years [18], but data on the persistence of ColdA risk are lacking. Education is crucial, as patients who are unaware of their condition's risks are more vulnerable to life-threatening complications. Key educational points include:

1. ***Trigger avoidance:*** Patients must be advised to exercise caution during activities involving complete water immersion, such as swimming in the sea, lake or pool. Importantly, avoiding all other cold triggers is often unnecessary; patients should avoid only those triggers that have previously caused reactions. For example, if cold food or drinks do not elicit reactions, there is probably no need for avoidance.
2. ***Recognition of early signs of ColdA:*** Patients must learn how to identify early clinical signs of ColdA. They should also be thoroughly instructed on when and how to self-administer an AAI.
3. ***Understanding of treatment options:*** High-risk patients should always carry AAIs and wear a medical alert bracelet. While second-generation H_1-antihistamines can be effective in managing itch and wheals, they are not substitutes for adrenaline in treating ColdA. Bronchodilators can offer relief from respiratory symptoms, especially for individuals with asthma. Glucocorticos-

teroids, although not typically used for immediate treatment, can be considered in post-ColdA management to reduce inflammation.

Consistent follow-ups with a specialist are essential for high-risk patients to ensure effective long-term management and monitoring of their condition.

Future research directions in ColdA

ColdA remains an intriguing yet understudied area amongst anaphylactic reactions. To improve our understanding of this unique condition and patient care, the following aspects need further research:

1. ***ColdA frequency and risk factors***: Comparative studies of ColdA prevalence and its associated risk factors in patients with $ColdU^T$ versus $ColdU^A$ are needed.
2. ***Cofactors***: ColdA is likely influenced by multiple factors, and identifying potential cofactors such as genetic predisposition, comorbidities, and environmental triggers could help understand its speed of onset and severity.
3. ***Laboratory features***: A comparative analysis of laboratory features between ColdU patients who experienced ColdA and those who did not could help identify potential biomarkers and clinical predictors of ColdA.
4. ***Serum tryptase levels***: Measuring serum tryptase levels immediately following ColdA could help establish a baseline for understanding MC and basophil activation in ColdA.

Conclusion

This review offers practical information for routine clinical practice and highlights the urgent need for establishing a universally accepted definition of ColdA. Furthermore, it emphasizes the necessity for further extensive research to elucidate its pathophysiology. Collective effort will be needed to develop effective management strategies and improve clinical outcomes for patients suffering from this challenging condition.

Author contributions M.B. conceived the idea for the manuscript, conducted the literature search, and drafted the manuscript. K.R. and R.A. critically reviewed and revised the manuscript. All authors have read and approved the final manuscript for submission.

Funding This research was supported by the Slovenian Research Agency (grant No. P3-0360).

Declarations

Competing interests M.B. is or recently was a speaker and/or advisor for Novartis outside the submitted work. K.R. is or recently was a speaker and/or advisor for Novartis and ALK outside the submitted work. R.A. has nothing to disclose.

Human and animal rights and informed consent This article does not contain any studies with human or animal subjects performed by any of the authors.

References

Papers of particular interest, published recently, have been highlighted as: • Of importance •• Of major importance

1. Jutel M, Agache I, Zemelka-Wiacek M, Akdis M, Chivato T, Del Giacco S, et al. Nomenclature of allergic diseases and hypersensitivity reactions: Adapted to modern needs: An EAACI position paper. Allergy. 2023;78:2851–74.
2. Muraro A, Roberts G, Worm M, Bilo MB, Brockow K, Fernandez Rivas M, et al. Anaphylaxis: guidelines from the European Academy of Allergy and Clinical Immunology. Allergy. 2014;69:1026–45.
3. Anagnostou K, Turner PJ. Myths, facts and controversies in the diagnosis and management of anaphylaxis. Arch Dis Child. 2019;104:83–90.
4. Ring J, Behrendt H. Anaphylaxis and anaphylactoid reactions. Classification and pathophysiology. Clin Rev Allergy Immunol. 1999;17:387–99.
5. Simons FE, Ardusso LR, Bilo MB, El-Gamal YM, Ledford DK, Ring J, et al. World allergy organization guidelines for the assessment and management of anaphylaxis. World Allergy Organ J. 2011;4:13–37.
6. •• Golden DBK, Wang J, Waserman S, Akin C, Campbell RL, Ellis AK, et al. Anaphylaxis: A 2023 practice parameter update. Ann Allergy Asthma Immunol. 2024;132:124-76. **This manuscript on anaphylaxis in general is the first to state that patients with cold urticaria have a higher likelihood of requiring treatment with adrenaline (epinephrine) autoinjectors**.
7. Kaplan MS, Jung SY, Chiang ML. Epinephrine autoinjector refill history in an HMO. Curr Allergy Asthma Rep. 2011;11:65–70.
8. Moller A, Henning M, Zuberbier T. Czarnetzki-Henz BM [Epidemiology and clinical aspects of cold urticaria]. Hautarzt. 1996;47:510–4.

9. Maltseva N, Borzova E, Fomina D, Bizjak M, Terhorst-Molawi D, Kosnik M, et al. Cold urticaria - What we know and what we do not know. Allergy. 2021;76:1077–94.
10. Bizjak M, Kosnik M, Terhorst-Molawi D, Dinevski D, Maurer M. Cold Agglutinins and Cryoglobulins Associate With Clinical and Laboratory Parameters of Cold Urticaria. Front Immunol. 2021;12:665491.
11. Bizjak M, Maurer M, Kosnik M, Terhorst-Molawi D, Zver S, Burmeister T, et al. Severe cold urticaria can point to an underlying clonal mast cell disorder. Allergy. 2021;76:2609–13.
12.•• Bizjak M, Kosnik M, Dinevski D, Thomsen SF, Fomina D, Borzova E, et al. Risk factors for systemic reactions in typical cold urticaria: Results from the COLD-CE study. Allergy. 2022;77:2185–99. **This large international study identified clinical risk factors for cold-induced anaphylaxis and provided critical insights for disease management.**
13. Juhlin L, Shelley WB. Role of mast cell and basophil in cold urticaria with associated systemic reactions. JAMA. 1961;177:371–7.
14. Fernando SL. Cold-induced anaphylaxis. J Pediatr. 2009;154:148-e1.
15.• Prosty C, Gabrielli S, Le M, Ensina LF, Zhang X, Netchiporouk E, et al. Prevalence, Management, and Anaphylaxis Risk of Cold Urticaria: A Systematic Review and Meta-Analysis. J Allergy Clin Immunol Pract. 2022;10:586–96 e4. **This is the first meta-analysis of the prevalence of anaphylaxis in cold urticaria.**
16.•• Bizjak M, Kosnik M, Dinevski D, Thomsen SF, Fomina D, Borzova E, et al. Adrenaline autoinjector is underprescribed in typical cold urticaria patients. Allergy. 2022;77:2224–9. **Findings of this international study revealed low adrenaline (epinephrine) prescription rates in cold urticaria patients and highlighted the insufficient treatment of cold-induced anaphylaxis.**
17. Maurer M, Metz M, Bindslev-Jensen C, Bousquet J, Canonica GW, Church MK, et al. Definition, aims, and implementation of GA(2) LEN Urticaria Centers of Reference and Excellence. Allergy. 2016;71:1210–8.
18. Magerl M, Altrichter S, Borzova E, Gimenez-Arnau A, Grattan CE, Lawlor F, et al. The definition, diagnostic testing, and management of chronic inducible urticarias - The EAACI/GA(2) LEN/EDF/UNEV consensus recommendations 2016 update and revision. Allergy. 2016;71:780–802.
19. Relvas M, Silva J, Alves F, Matos A, Bizjak M, Goncalo M. Localized cold urticaria: an unusual form of cold urticaria. J Eur Acad Dermatol Venereol. 2022;36:e133–5.
20. Jain SV, Mullins RJ. Cold urticaria: a 20-year follow-up study. J Eur Acad Dermatol Venereol. 2016;30:2066–71.
21. Katsarou-Katsari A, Makris M, Lagogianni E, Gregoriou S, Theoharides T, Kalogeromitros D. Clinical features and natural history of acquired cold urticaria in a tertiary referral hospital: a 10-year prospective study. J Eur Acad Dermatol Venereol. 2008;22:1405–11.
22. Alangari AA, Twarog FJ, Shih MC, Schneider LC. Clinical features and anaphylaxis in children with cold urticaria. Pediatrics. 2004;113:e313-7.
23. Doeglas HM, Rijnten WJ, Schroder FP, Schirm J. Cold urticaria and virus infections: a clinical and serological study in 39 patients. Br J Dermatol. 1986;114:311–8.
24. Neittaanmaki H. Cold urticaria. Clinical findings in 220 patients. J Am Acad Dermatol. 1985;13:636–44.
25. Kulthanan K, Tuchinda P, Chularojanamontri L, Kiratiwongwan R. Cold Urticaria: Clinical Features and Natural Course in a Tropical Country. Allergy Asthma Immunol Res. 2019;11:538–47.
26. Deza G, Brasileiro A, Bertolin-Colilla M, Curto-Barredo L, Pujol RM, Gimenez-Arnau AM. Acquired cold urticaria: Clinical features, particular phenotypes, and disease course in a tertiary care center cohort. J Am Acad Dermatol. 2016;75(918–24):e2.
27. Siebenhaar F, Degener F, Zuberbier T, Martus P, Maurer M. High-dose desloratadine decreases wheal volume and improves cold provocation thresholds compared with standard-dose treatment in patients with acquired cold urticaria: a randomized, placebo-controlled, crossover study. J Allergy Clin Immunol. 2009;123:672–9.
28. Mathelier-Fusade P, Aissaoui M, Bakhos D, Chabane MH, Leynadier F. Clinical predictive factors of severity in cold urticaria. Arch Dermatol. 1998;134:106–7.
29. Wanderer AA, Grandel KE, Wasserman SI, Farr RS. Clinical characteristics of cold-induced systemic reactions in acquired cold urticaria syndromes: recommendations for prevention of this complication and a proposal for a diagnostic classification of cold urticaria. J Allergy Clin Immunol. 1986;78:417–23.
30. Ginter K, Ahsan DM, Bizjak M, Krause K, Maurer M, Altrichter S, et al. Cryoglobulins, Cryofibrinogens, and Cold Agglutinins in Cold Urticaria: Literature Review, Retrospective Patient Analysis, and Observational Study in 49 Patients. Front Immunol. 2021;12:675451.
31. Maurer M, Fluhr JW, Khan DA. How to Approach Chronic Inducible Urticaria. J Allergy Clin Immunol Pract. 2018;6:1119–30.
32. Paulino M, Costa C, Neto M, Pedro E. Cold Urticaria. Characterizing the population from an urticaria outpatient clinic. Actas Dermosifiliogr (Engl Ed). 2021 May 28:S1578–2190(21)00182–7.
33. Yee CSK, El Khoury K, Albuhairi S, Broyles A, Schneider L, Rachid R. Acquired Cold-Induced Urticaria in Pediatric Patients: A 22-Year Experience in a Tertiary Care Center (1996–2017). J Allergy Clin Immunol Pract. 2019;7(1024–31):e3.
34. Deza G, Mensa-Vilaro A, March-Rodriguez A, Sanchez S, Pujol RM, Arostegui JI, et al. Acquired Cold Urticaria vs. Autoinflammatory Diseases, Genetic and Clinical Profile and Differential Diagnosis: Study of a Cohort of Patients in a Tertiary Reference Centre. Acta Derm Venereol. 2019;99:1071–7.
35. Stepaniuk P, Vostretsova K, Kanani A. Review of cold-induced urticaria characteristics, diagnosis and management in a Western Canadian allergy practice. Allergy Asthma Clin Immunol. 2018;14:85.
36. Azkur D, Civelek E, Toyran M, Misirlioglu ED, Erkocoglu M, Kaya A, et al. Clinical and etiologic evaluation of the children with chronic urticaria. Allergy Asthma Proc. 2016;37:450–7.
37. Sanchez J, Amaya E, Acevedo A, Celis A, Caraballo D, Cardona R. Prevalence of Inducible Urticaria in Patients with Chronic Spontaneous Urticaria: Associated Risk Factors. J Allergy Clin Immunol Pract. 2017;5:464–70.
38. Tomei L, Saretta F, Arasi S, Sarti L, Licari A, Giovannini M, et al. Cold Anaphylaxis in Children: Italian Case Series and Review of the Literature. Diseases. 2023;11:143.
39. Kemp SF, Lockey RF. Anaphylaxis: a review of causes and mechanisms. J Allergy Clin Immunol. 2002;110:341–8.
40. Simons FE, Frew AJ, Ansotegui IJ, Bochner BS, Golden DB, Finkelman FD, et al. Risk assessment in anaphylaxis: current and future approaches. J Allergy Clin Immunol. 2007;120:S2-24.
41. Williams KW, Sharma HP. Anaphylaxis and urticaria. Immunol Allergy Clin North Am. 2015;35:199–219.
42. Sala-Cunill A, Cardona V, Labrador-Horrillo M, Luengo O, Esteso O, Garriga T, et al. Usefulness and limitations of sequential serum tryptase for the diagnosis of anaphylaxis in 102 patients. Int Arch Allergy Immunol. 2013;160:192–9.

43. Yegit OO, Aslan AF, Coskun R, Karadag P, Toprak ID, Can A, et al. Comparison of recent anaphylaxis diagnostic criteria in real life: Can more patients be diagnosed as having anaphylaxis? World Allergy Organ J. 2023;16:100810.
44. Hochstadter EF, Ben-Shoshan M. Cold-induced urticaria: challenges in diagnosis and management. BMJ Case Rep. 2013 Jul 8;2013:bcr2013010441.
45. Claudy A. Cold urticaria. J Investig Dermatol Symp Proc. 2001;6:141–2.
46. Alrafiaah AS, Netchiporouk E, Ben-Shoshan M. Cold-induced anaphylaxis triggered by drinking cold water. Allergol Immunopathol (Madr). 2024;52:45–7.
47. Maciag MC, Nargozian C, Broyles AD. Intraoperative anaphylaxis secondary to systemic cooling in a pediatric patient with cold-induced urticaria. J Allergy Clin Immunol Pract. 2018;6:1394–5.
48. Lockhart CH, Brownrigg JC. Anesthetic hazards of cold urticaria. Anesthesiology. 1973;38:96–7.
49. Park HJ, Park SY, Lee SH, Kim GH, Yang JE, Yoon SY, et al. Cold-induced systemic reactions caused by infusion of intravenous fluid. Acta Derm Venereol. 2013;93:469–70.
50. Pałgan K. Mast Cells and Basophils in IgE-Independent Anaphylaxis. Int J Mol Sci. 2023;24:12802.
51. Bilo MB, Martini M, Tontini C, Corsi A, Antonicelli L. Anaphylaxis. Eur Ann Allergy. Clin Immunol. 2021;53:4–17.
52. Murphy GF, Austen KF, Fonferko E, Sheffer AL. Morphologically distinctive forms of cutaneous mast cell degranulation induced by cold and mechanical stimuli: an ultrastructural study. J Allergy Clin Immunol. 1987;80:603–11.
53. Lawlor F, Kobza Black A, Breathnach AS, McKee P, Sarathchandra P, Bhogal B, et al. A timed study of the histopathology, direct immunofluorescence and ultrastructural findings in idiopathic cold-contact urticaria over a 24-h period. Clin Exp Dermatol. 1989;14:416–20.
54. Church MK, Kolkhir P, Metz M, Maurer M. The role and relevance of mast cells in urticaria. Immunol Rev. 2018;282:232–47.
55. Maurer M, Church MK, Goncalo M, Sussman G, Sanchez-Borges M. Management and treatment of chronic urticaria (CU). J Eur Acad Dermatol Venereol. 2015;29(Suppl 3):16–32.
56. Weller K, Gimenez-Arnau A, Grattan C, Asero R, Mathelier-Fusade P, Bizjak M, et al. The Chronic Urticaria Registry: rationale, methods and initial implementation. J Eur Acad Dermatol Venereol. 2021;35:721–9.
57. Tomasiak-Lozowska MM, Klimek M, Lis A, Moniuszko M, Bodzenta-Lukaszyk A. Markers of anaphylaxis - a systematic review. Adv Med Sci. 2018;63:265–77.
58. Ensina LF, Min TK, Felix MMR, de Alcantara CT, Costa C. Acute Urticaria and Anaphylaxis: Differences and Similarities in Clinical Management. Front Allergy. 2022;3:840999.
59. Zhou B, Li J, Liu R, Zhu L, Peng C. The Role of Crosstalk of Immune Cells in Pathogenesis of Chronic Spontaneous Urticaria. Front Immunol. 2022;13:879754.
60. Varricchi G, Marone G. Mast Cells: Fascinating but Still Elusive after 140 Years from Their Discovery. Int J Mol Sci. 2020;21:464.
61. Maurer M, Altrichter S, Schmetzer O, Scheffel J, Church MK, Metz M. Immunoglobulin E-Mediated Autoimmunity Front Immunol. 2018;9:689.
62. Houser DD, Arbesman CE, Ito K, Wicher K. Cold urticaria. Immunologic studies Am J Med. 1970;49:23–33.
63. Kaplan AP, Garofalo J, Sigler R, Hauber T. Idiopathic cold urticaria: in vitro demonstration of histamine release upon challenge of skin biopsies. N Engl J Med. 1981;305:1074–7.
64. Sherman WB, Seebohm PM. Passive transfer of cold urticaria. J Allergy. 1950;21:414–24.
65. Akiyama T, Ushijima N, Anan S, Takahashi I, Yoshida H. A case of cold urticaria due to a serum factor belonging to the IGE class. J Dermatol. 1981;8:139–43.
66. Kaplan AP. The pathogenic basis of urticaria and angioedema: recent advances. Am J Med. 1981;70:755–8.
67. Boyce JA. Successful treatment of cold-induced urticaria/anaphylaxis with anti-IgE. J Allergy Clin Immunol. 2006;117:1415–8.
68. Freichel M, Almering J, Tsvilovskyy V. The Role of TRP Proteins in Mast Cells. Front Immunol. 2012;3:150.
69. Stoevesandt J, Sturm GJ, Bonadonna P, Oude Elberink JNG, Trautmann A. Risk factors and indicators of severe systemic insect sting reactions. Allergy. 2020;75:535–45.
70. Kosnik M, Korosec P. Venom immunotherapy: clinical efficacy, safety and contraindications. Expert Rev Clin Immunol. 2015;11:877–84.
71. Selb J, Rijavec M, Erzen R, Zidarn M, Kopac P, Skerget M, et al. Routine KIT p.D816V screening identifies clonal mast cell disease in patients with Hymenoptera allergy regularly missed using baseline tryptase levels alone. J Allergy Clin Immunol. 2021;148:621–6 e7.
72. Kacar M, Rijavec M, Selb J, Korosec P. Clonal mast cell disorders and hereditary alpha-tryptasemia as risk factors for anaphylaxis. Clin Exp Allergy. 2023;53:392–404.
73. Valent P. Risk factors and management of severe life-threatening anaphylaxis in patients with clonal mast cell disorders. Clin Exp Allergy. 2014;44:914–20.
74. Akin C. Mast cell activation syndromes. J Allergy Clin Immunol. 2017;140:349–55.
75. Worm M, Francuzik W, Renaudin JM, Bilo MB, Cardona V, Scherer Hofmeier K, et al. Factors increasing the risk for a severe reaction in anaphylaxis: An analysis of data from The European Anaphylaxis Registry. Allergy. 2018;73:1322–30.