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## Features of anesthetic care for patients with cold urticaria (literature review)

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**Abstract.** Cold urticaria (CU) is an allergic reaction that manifests itself as hives-like rashes or red spots in response to general or local cooling of the body. The disease can be acquired or hereditary, and in the cold season it can affect all segments of the population. This pathological condition, at first glance, does not seem to be a very dangerous variant of a local cold injury, but in persons who are prone to exposure to low temperatures, especially with a burdened cold history, it may be accompanied by chronicity of the process and complicated by neurovasculitis, obliterating endarteritis and secondary Raynaud's syndrome, may decrease the quality of life of the victims and become a cause of disability. The pathophysiology of CU is largely unknown, but it is likely to be related to immunoglobulin E (IgE) and mast cell activation. Cooling has been reported to induce the release of neutrophilic and eosinophilic chemotactic factors, prostaglandin D<sub>2</sub>, and tumor necrosis factor (TNF- $\alpha$ ). Less common immunologic findings in patients with CU include cryoglobulinemia consisting of monoclonal IgG and mixed IgG/IgM and IgG/IgA cryoglobulin types. The mechanisms of development of CU are mainly determined by the formation of cryoglobulins (cold hemolysins) and subsequent degranulation of mast cells. The diagnosis of CU depends on the patient's history and the results of cold provocation tests. Patients with CU are recommended first of all not to overcool, to take warm showers, to wear warm clothes and a hat, and not to consume cold food and drinks. Treatment options include second-generation H<sub>1</sub> antihistamines and glucocorticosteroids. New promising option is omalizumab, a humanized monoclonal antibody derived from a recombinant DNA molecule that targets and selectively binds to circulating IgE and affects mast cells function. In patients with CU undergoing general anesthesia, premedication including antihistamines and corticosteroids is recommended, along with strict maintenance of perioperative normothermia.

**Keywords:** local cold injury, cold urticaria, diagnosis, treatment, anesthesia

Frost pinched the young man's reddened cheeks.  
D. Pozhodzhuk, Crimean lighthouse. 04.02.2023

Cold urticaria (CU) is an allergic reaction that manifests itself as hives or red spots in response to general or local cooling of the body. The disease can be acquired or he-

reditary, and in the cold season can affect all segments of the population [1].

CU was first described by Frank J.P. in 1792. Boudron H. in 1866 reported a patient with CU and systemic symptoms after hypothermia. Blanches M. later reported a woman with increased sensitivity to cold objects

and drinks [2]. People who have a tendency to develop cold allergies are often diagnosed with CU [3].

Acquired CU is a common subtype of physical urticaria characterized by the development of skin reactions such as redness and burning, or the occurrence of angioedema caused by the release of histamine, leukotrienes, and other proinflammatory mediators from mast cells after exposure to cold. Systemic anaphylaxis occurs in one out of three patients susceptible to CU [4]. Acquired CU is the fourth most common type of persistent urticaria after chronic spontaneous, dermatographic, and cholinergic urticaria.

In most patients, acquired cold allergy is idiopathic, but in rare cases it may result from infections, neoplasms, or autoimmune diseases that require immediate treatment. Acquired cold allergy mainly occurs in young people and is twice as often diagnosed in women than in men. The disease can begin at any age, but mostly it occurs during the second to fourth decade of life [2]. In the absence of treatment, it lasts an average of 4–5 years, with remission or improvement of symptoms in 50 % of patients within 5 years. The incidence of CU is estimated at 0.05 % [5] with a higher prevalence in northern climates [6].

CU accounts for 3 % to 33.8 % of cases of physical urticaria, with a higher incidence in cold climates [4]. The more pronounced the clinical symptoms, the more severe this condition is. Undoubtedly, the severity of clinical manifestations depends on the area of cooling and the cooling factor. In people who are very sensitive to cold, cooling a large body surface can cause anaphylactoid reactions. The cardiovascular system is the most vulnerable extracutaneous system, followed by the respiratory and gastrointestinal systems [4].

Patients also have disorders of the cardiovascular and respiratory systems (headache, dizziness, shortness of breath, tachycardia, decreased blood pressure, etc.); oropharyngeal angioedema; gastrointestinal symptoms (abdominal pain, nausea, vomiting, diarrhea, painful defecation) may occur after eating cold food, but most often they occur due to prolonged contact with cold during exposure in water [5]. Visceral complications are also typical — chronic hepatitis, glomerulonephritis, peripheral neuropathies. Lymphoproliferative disorders play a role in the pathogenesis, up to malignancy with the development of  $\beta$ -cell non-Hodgkin's lymphoma. A high risk of cold arthritis is associated with contact of large areas of the skin with cold, for example, when swimming in open water, when introducing cool infu-

sion solutions or during long surgical interventions. Cold-induced acute allergic coronary Kounis syndrome was reported in a patient with cold after swimming in the sea [2]. Often, the maximum manifestations are noted when warming up the affected areas of the body [7].

The severity of clinical manifestations depends on the cooling area and the cold stimulus [2]. Cases of death caused by exposure to cold (after immersing such a patient in water) are described. CU has been reported to be associated with viral or bacterial infections (borreliosis, hepatitis, infectious mononucleosis, syphilis, and HIV), medication, hymenoptera bites, hematologic malignancies, and immunotherapy [6, 7, 8]. In addition, cases associated with *Helicobacter pylori* colonization, acute toxoplasmosis, and other parasitic infestations have been described. Infections of the upper respiratory tract, teeth, and genitourinary tract may also be associated with CU [5]. In patients with CU, a wide range of individual critical temperature thresholds is observed from 4 °C to 27 °C. Common cold triggers include contact with cold objects or surfaces, cold water (swimming or a cold shower), low ambient temperature (cold season, air conditioning), wind, and consumption of cold foods (ice cream) and beverages [2].

The presumed reaction mechanism is a congenital defect in serotonin metabolism [8, 9]. The mediated effect of the neuro-endocrine system is clearly manifested in cold allergy, when the action on the regulatory center of the hypothalamus causes a shift in the synthesis of hormones, which stimulates the development of an allergic reaction [7].

The pathophysiology of CU is largely unknown, but it is likely to be related to immunoglobulin E (IgE) and mast cell activation [5, 11, 12]. Cold exposure can lead to the formation of de novo autoantigens that can induce an IgE response and, in sensitized individuals, subsequently cause IgE-dependent mast cell degranulation (IgE-mediated autoimmunity) [8]. At the moment, cold-dependent skin antigens have not been identified, and there is no direct evidence to support this theory. However, it is supported by several lines of circumstantial evidence. Although the initial events that translate the cold stimulus into a sequence of molecular and cellular changes in the skin of patients with cold idiosyncrasy remain unclear, the process is likely immunologically mediated [2]. In addition, the following mechanisms are involved in the pathogenesis of CU:

- activation of the complement system and formation of anaphylotoxins C3a and C5a;

- the formation of IgE class autoantibodies to the skin antigen induced by exposure to cold.

However, purified plasma IgE functions as a monomer, does not polymerize in the cold, which refutes the IgE cryoprotein hypothesis [2]. Mutations cause clonal damage to the mast cells and cause severe anaphylaxis in patients with systemic mastocytosis [9, 10]. Type IIb autoimmunity with mast cell targeting and activation of autoantibodies may also be involved [2]. It is believed that the symptoms of urticaria are primarily related to the activation of the skin's mast cells. However, in recent years, data has appeared that emphasize the possible role of blood coagulation in the pathophysiology of this disease. In some patients, in response to exposure to cold factors, primarily cold air, there may be reactions that clinically resemble the manifestations of sinusitis, conjunctivitis, and bronchial asthma, although CU can coexist with other types of urticaria [13, 14]. Other issues relate to the underlying mechanisms of dermal mast cell degranulation, which is a central mechanism in cold-induced blistering and angioedema formation. The kinetics and significance of other mediators are less clearly defined. Cooling has been reported to induce the release of neutrophilic and eosinophilic chemotactic factors, prostaglandin D<sub>2</sub>, and tumor necrosis factor (TNF- $\alpha$ ) [2].

Less common immunologic findings in patients with CU include cryoglobulinemia consisting of monoclonal IgG and mixed IgG/IgM and IgG/IgA cryoglobulin types. Antibodies against lamin B, decreased C1-esterase and C4 inhibitors, and elevated platelet-activating factor 4 [5].

The mechanisms of development of CU are mainly determined by the formation of cryoglobulins (cold hemolysins) and subsequent degranulation of mast cells [2]. Cryoglobulins are immunoglobulins that undergo reversible precipitation at low temperatures and dissolve when heated [2]. Cold agglutinins and cryoglobulins in a subpopulation of patients with CU are related to the course and pathogenesis of the disease [9, 10]. Cryoglobulinemia is characterized by the appearance of circulating cryoglobulins that precipitate in the cold with their deposition in the walls of small vessels (capillaries, arterioles, and venules) with symptoms of systemic vasculitis. With cryoglobulinemia, patients have an increased level of immunoglobulins in the blood serum, which causes them to undergo reversible precipitation at lower temperatures [4]. With cryoglobulinemia, four vascular lesions are noted: clogging of small and large vessels in those with a high level of type I or II cryoglob-

ulins; mild thrombosis of small arteries and arterioles; endothelial edema, membrane proliferation and thickening, and leukocytoclastic vasculitis.

Cryopyrin-associated periodic syndromes belong to a group of rare autoinflammatory diseases: familial cold-induced autoinflammatory syndrome (FCAS), a rare genetic disease caused by mutations in inflammatory pathways that lead to increased production of IL-1 $\beta$ . It is characterized by CU, arthralgias, fever, renal amyloidosis, sensorineural deafness, conjunctivitis, chronic aseptic meningitis and intellectual disability [4].

Within minutes of skin exposure to cold air, liquids, or objects, patients with CU develop an itchy urticarial rash that may progress to angioedema and anaphylaxis [3]. With local CU, a blister and/or angioedema after exposure to cold cover only a limited surface of the skin. Cold erythema is accompanied by pain and erythema of the skin area that has experienced cooling, without the development of typical blisters and itching; at the same time, a test with ice gives a positive result [15, 16].

The development of CU indicates a predisposition to future episodes, although an episode does not necessarily occur with every exposure to cold [15, 16].

CU manifests itself as a localized or systemic rash within a few minutes after exposure to cold. Most often, the disease is manifested by purpura, weakness, pain in the joints, paleness or cyanosis, and sharp pains in the fingers and toes when leaving the house in cold weather. Patients experience burning, itching, erythema, blistering and/or swelling of the skin within a few minutes of exposure to cold water / icy air. As a rule, these symptoms appear mainly on the face, hands; often reach a maximum during warming of cooled parts of the body and disappear within 30–60 minutes. One of the body's reactions to exposure to low temperatures is cold erythema, characterized by a small-celled widespread rash without an urticarial component, swelling of the lips, tongue, and pharynx may occur. Sometimes CU can be accompanied by a persistent urticarial rash, which usually appears a few minutes after exposure to cold, but persists for a week or longer. Another variant of CU is the occurrence of urticaria in a different place — around the cooled area of the skin, and not directly where the skin was exposed to cold (the so-called reflex CU).

*Reflex CU* is a general or local reaction to cold, similar to cholinergic urticaria. Sometimes it occurs only when the whole body is cooled. A local reaction to the cold is manifested by a rash that occurs around the cooled area

of skin, while the skin that has been directly exposed to the cold is not affected.

*Familial CU* is a rare form of urticaria inherited in an autosomal dominant pattern. Spot-papular rash and burning are characteristic, occurring 0.5–3 hours after exposure to cold. Systemic manifestations are possible: fever, dyspnea, joint pain, leukocytosis. A rare form of the disease is described, in which urticaria occurs 20–30 hours after exposure to cold. Since the rash is accompanied by itching and burning, the diagnosis of chronic idiopathic urticaria is often mistaken. It is known that the ability to form cryoglobulins can be due to hereditary predisposition and/or the presence of infectious factors. In connection with this, CU can be hereditary (familial) and acquired. Hereditary CU is a disease with an autosomal dominant type of inheritance, which manifests itself in the first months of life. There is an immediate form, which is characterized by the appearance of hot spots or nodules (only not blisters!); accompanied by chills, fever, arthralgia, myalgia, headache. Leukocytosis is observed in the blood. The delayed form is characterized by the appearance of blisters within 9–18 hours after exposure to cold, which disappear after 2–3 days. CU with permanent blisters is also observed, which is characterized by the appearance of blisters a few minutes after exposure to cold and persists for a week [8].

*Cold erythema* — manifested by reddening of the skin (erythema). This form of the disease is characterized by severe soreness of the affected areas of the skin [8].

*Cold dermatitis* — the skin is very itchy and flaky. If the disease has acquired a rather severe form, swelling of the whole body can be observed. Some authors classify cold dermatitis into primary, i.e., idiopathic, and secondary, due to underlying causes, such as autoimmune and lymphoproliferative diseases, viral and bacterial infections, hymenoptera bites, taking certain medications or food products. However, the evidence for a causal relationship between these conditions and cold dermatitis is weak, questioning the usefulness of this classification for clinical practice [2].

*Cold rhinitis* differs from the common cold in that the feeling of nasal congestion occurs exclusively in the cold. As soon as a person suffering from this form of cold allergy enters a warm room, all symptoms immediately disappear.

*Cold conjunctivitis* — in the cold there is a strong lacrimation, as well as tearing in the eyes. Do not confuse the described symptoms with the body's natural protection against cold and windy weather, which do not cause

significant discomfort and quickly disappear in a warm environment.

*Chronic CU (CCU)* — this form of the disease is characterized by an acute onset, intense itching of open areas of the skin of the face, hands, and sometimes the entire surface of the body. Soon there is skin swelling at the places of itching, which forms into a blister. Then there is a rash with intense redness of certain areas of the skin, similar to the consequences of mosquito bites or stinging nettle rash. In severe forms of the disease, there is fever, general malaise, pain in the joints and muscles, palpitations, pronounced weakness. CCU is characterized by the presence of blisters that recur for a period exceeding 6 weeks after exposure to cold irritants [4]. The exacerbation of the disease can last for several weeks and even months, throughout the cold period of the year [6]. Chronic urticaria can be divided into physically induced and idiopathic [4].

The recurrent form of urticaria is characterized by seasonality: autumn, winter, early spring. Year-round exacerbations occur when the skin is exposed to cold water.

*Muckle — Wells syndrome* — a generalized inflammatory reaction to cold air or damp, humid weather, characterized by the appearance of itchy rashes with a diameter of 0.2–3 cm, which persist for 5–24 hours; polyarthritides (joint syndrome can be presented from short cases of arthralgia to relapses of arthritis of large joints); conjunctivitis; an increase in temperature (not always), leukocytes and the level of C-reactive protein in the blood; later, such patients may develop renal amyloidosis. There are no cryoglobulins and cold agglutinins in the blood; in some such patients, the ice/cold water challenge test may be negative, while after exposure to cold air they develop a rash and itchy skin. Vasodilation, tissue infiltration by neutrophils, monocytes and macrophages are histologically detected (as in other types of urticaria). In addition, Muckle — Wells syndrome is characterized by the progression of sensorineural deafness. It is possible that some patients with renal amyloidosis and sensorineural deafness have inaccurate diagnoses due to the latent course of the autoinflammatory syndrome. Also, attacks in Muckle — Wells syndrome can be provoked, on the contrary, by exposure to high temperatures, stress, and intense physical exertion. Usually, the disease begins in childhood, but cases have also been described in adults.

The diagnosis of CU depends on the patient's history and the results of cold provocation tests. Second-gener-



ation H<sub>1</sub>-antihistamines and systemic glucocorticoids should be discontinued at least 3 and 7 days before the study. A cube of melting ice in a thin plastic bag or a non-latex medical glove is pressed to the forearm for 5 minutes, after which a test (Duncan test) is performed 10 minutes after the end of cold stimulation. A positive result is a specific appearance of a raised red urticaria, sometimes with itching formations in the area of contact with ice [2, 13, 14], which can go beyond the limits of cold contact.

A test with water in the case of aquagenic urticaria can be carried out by immersing a part of the body in water with a temperature of 37 °C or applying a wet towel for a few minutes to the most vulnerable area of the skin [13, 14]. Siebenhaar et al. estimated the sensitivity of the ice cube test to be 83 % and the specificity to be 100 % [1, 5]. Routine testing with cold compresses or cold water baths is not recommended.

A cold test and determination of the threshold levels of beta-glucocerebrosidase, C-reactive protein and cryoproteins are performed in order to rule out other diseases, especially infectious ones [15, 16, 17].

However, although these techniques aid in diagnosis, they do not provide information about the thresholds of temperature and stimulation time at which patients begin to develop symptoms. This is very important, as it allows to determine the severity of the disease and control the effectiveness of treatment [18, 19, 20].

Cooling of venous blood: after obtaining plasma or serum, it is cooled at 4–5 °C for several hours (test for the presence of cryoglobulins) — if cryoglobulins are present, precipitates are observed after cooling, which disappear after warming at room temperature.

It should be noted that patients in whom blisters appear earlier than in 3 minutes have a high risk of developing severe systemic reactions. In 20 % of patients, skin tests with an ice cube can be negative, so a test using water with a temperature of +7 °C can be more illustrative [8].

Performing physical exercises for 15 minutes in the cold (+4 °C) is carried out in case of suspicion of cholinergic urticaria caused by exposure to cold. General cooling (staying in a cold room at +4 °C without clothes for 10–20 minutes) is performed in the diagnosis of systemic CU, for a positive result the appearance of urticaria and/or edema within 10–20 minutes is characteristic (with the hereditary form, the characteristic appearance spots or blisters, not urticaria, in the absence of itching) [8].

Patients with CU are recommended first of all not to overcool, to take warm showers, to wear warm clothes

(made of cotton or linen) and a hat, and not to consume cold food and drinks. Such patients are prohibited from swimming in the sea, exercising in the cold [5, 13, 14]. Before leaving the house, patients with CU should apply special products that protect the skin from the effects of cold (“Uriage”, “Mustela”, etc.) on exposed parts of the body (face, hands, lips).

Second-generation H<sub>1</sub> antihistamines such as bilastine, desloratadine, cetirizine hydrochloride (Allertec) and rupatadine exert their biological effects by stabilizing the histamine H<sub>1</sub> receptor (H<sub>1</sub>R) in its inactive state (inverse agonism); in licensed and high doses these drugs are the first and second line of CU treatment [2, 8, 15, 16, 21–23]. If there is no effect, glucocorticosteroids are used [2, 23].

Omalizumab is a humanized monoclonal antibody derived from a recombinant DNA molecule that targets and selectively binds to circulating IgE and affects mast cells/basophil function [2]. Omalizumab prevents the binding of IgE to the FcεRI receptor, thereby reducing the amount of free IgE. Treatment of patients with CU with omalizumab leads to a significant decrease in the number of FcεRI receptors on the surface of basophils and the release of histamine from basophils. In patients treated with omalizumab after stimulation with an allergen, their number decreases by approximately 90 %, compared to the indicators before treatment. The levels of free IgE in the serum decrease proportionally to the dose already 1 hour after the first injection and are at a constant level during the period between the administration of successive doses. Omalizumab may be a powerful adjunct in the treatment of CU in patients who have failed maximal antihistamine therapy. Initiation of omalizumab can lead to symptom relief, improved quality of life, and helps prevent anaphylaxis [6, 11, 20, 22, 24].

The drug was effective even at doses of 150 to 300 mg per month regardless of the level of total serum IgE. Omalizumab demonstrated a sufficient level of safety when used in patients with CU [13, 14].

Leukotriene receptor antagonists, anti-inflammatory agents (diaminodiphenyl sulfone, sulfasalazine, hydroxychloroquine, colchicine), tricyclic antidepressants (doxepin) and immunosuppressants (azathioprine, methotrexate, cyclophosphamide, sirolimus, mycophenolate mofetil) have shown promising results in the treatment of patients with resistance to antihistamines, however the use of these drugs is limited by their potential toxicity and low level of evidence [2, 25]. Various agents targeting interleukin-1 and interleukin-1β have

been used in patients with CU caused by FCAPS with positive results. All patients with CU should be provided with epinephrine auto-injectors for emergency situations [4].

There are reports of therapeutic plasmapheresis with heparin cryofractionation of the obtained plasma followed by its return to compensate for the loss of circulating blood volume during subsequent plasmapheresis sessions. The technology of cascade plasmapheresis is also used with success. Ultraviolet B therapy has been reported to be effective in some cases. Elimination measures, patient education, and treatment according to existing algorithms can significantly improve the quality of life of patients, which is the first priority in the treatment of any chronic disease [13, 14].

Patients with a positive test for cold agglutinins had a higher incidence of angioedema caused by ingestion of cold foods or beverages [9, 10]. Treatment for systemic reactions to cold is the same as for systemic anaphylactic reactions [8, 26]. Cases of sudden life-threatening episodes of anaphylactic reactions to cold require immediate administration of epinephrine to the patient (ideally — by autoinjector). Patients at risk of oropharyngeal edema or shock-like reactions should be equipped with an emergency kit containing corticosteroids, antihistamines, and an epinephrine injector [5].

Antibiotics should be considered in some patients. Some patients with an acute disease benefit from such treatment, even if the infection cannot be detected and identified [5].

Prophylactically, antihistamines are prescribed (especially cyprahiptadine or doxepin).

Hardening can be effective, which is carried out as follows: one upper limb is immersed in cold water at a temperature of about 15 °C for 5 minutes, every day for several days, when the reaction decreases, the time the limb is in the water is increased, then both upper limbs are immersed; after a few days, the upper and lower limbs are immersed, and lastly, they begin to immerse the face.

Cold desensitization also reduces symptoms. However, the initial treatment should be carried out under the supervision of a doctor, as it can cause anaphylaxis [23, 27].

CU is a rare and potentially fatal disease that presents a challenge to anesthesiologists and is easily underestimated. Adequate preoperative management is critical to prevent catastrophic events such as angioedema or anaphylaxis. The risk of a severe reaction can be

reduced by careful planning of perioperative normothermia and preoperative prophylactic use of H1 and H2 receptors blockers and corticosteroids. Normothermia is best achieved with one or more blankets with forced air heating with careful control of internal and ambient temperature in the operating room. Avoiding potentially allergenic medications can make it easier to identify the true cause of any reaction. These aggressive measures minimize perioperative morbidity and mortality in patients with CU [4].

In patients with CU undergoing general anesthesia, there is a risk of anaphylaxis if perioperative normothermia is not strictly maintained. Redistribution of central body temperature to the periphery occurs within the first 30 minutes or an hour after the induction of general or regional anesthesia due to sympathoplegia and vasodilatation [28]. This can lead to a 1–2 °C drop in core temperature if no effort is made to rewarm, eliminate or reduce the core-peripheral body temperature gradient. A further decrease in temperature occurs due to a violation of thermoregulation of the hypothalamus by anesthetics and a decrease in the shivering threshold [29, 30]. In this case, normothermia can be achieved with warm blankets with forced ventilation, intravenous fluids warmed to 40 °C with an integrated fluid heater, and careful control of ambient room temperature [4, 31].

Literature on perioperative treatment of CU is scarce. In most reported cases, premedication included antihistamines (both H1- and H2-blockers) and a single dose of corticosteroids. When conducting general anesthesia for a patient with CU, the primary task is to prevent both the initial and the final mechanism of anaphylaxis. To this end, famotidine, diphenhydramine, and a single dose of hydrocortisone administered intravenously 30 minutes before induction can inhibit immune histamine release. In addition, drugs that cause histamine release should be avoided if possible. Although histamine release is not known to cause CU, urticaria from any source can confound a patient's clinical presentation. Neuromuscular blocking agents, such as rocuronium, cause up to 58.2 % of anaphylaxis related to anesthesia. In a study evaluating the incidence of anaphylaxis during anesthesia, rocuronium was associated with 56 % of cases, succinylcholine with 21 %, and vecuronium with 11 % [4, 32].

Morphine, codeine, and some synthetic opioids are known to increase histamine levels independently of IgE antibodies. Anesthetics such as propofol and thio-pental also sometimes cause anaphylaxis. Other agents used in the operating room that can provoke an immune

response include midazolam, ketamine, chlorhexidine, colloids, protamine sulfate, and local anesthetics such as lidocaine [33, 34]. Although it is impossible to completely avoid the risk of a histamine- or immune-mediated reaction, minimizing the risk can prevent the confusion that can occur as a result of a reaction unrelated to cooling [4]. A cold stimulus can induce an immune response without significantly lowering core temperature. For example, with CU of the delayed type, symptoms develop 24–72 hours after exposure to the cold agent, even after rewarming. Premedication with diphenhydramine, famotidine, and hydrocortisone may suppress the immune response [25].

H<sub>1</sub>-antihistamines of the second generation in standard doses are the first-line therapy for the treatment and prevention of chronic urticaria. Many first-generation antihistamines have shown similar efficacy, but their sedative, antimuscarinic, and anti-alpha-adrenergic properties make them unfavorable for outpatient treatment. Because chronic urticaria is difficult to control, especially in patients who do not respond to first-line therapy, no specific treatment protocol exists. Some studies have successfully used adjuncts to H<sub>1</sub> blockers. Doses of H<sub>1</sub>-antihistamine drugs, four times the usual dose, increased the effectiveness of preventive and abortive treatment from 45 % to more than 60 %. The results of studies evaluating the combination of H<sub>1</sub> and H<sub>2</sub> receptor antagonists are conflicting, although this combination continues to be superior to other second-line treatment options [25]. Limited use of corticosteroids as a second-line agent has shown promising results, but is recommended only as short-term abortive and prophylactic therapy due to side effects of chronic use [25].

CU, at first glance, does not seem to be a very dangerous variant of local cold injury, but in persons who are exposed to cold, especially with a aggravated medical history, it can be accompanied by a chronic process and be complicated by neurovasculitis, obliterating endarteritis and secondary Raynaud's syndrome, it can affect the quality of life and cause disability. The authors hope that the information provided will be useful for a doctor of any profile and will contribute to the optimization of the diagnostics and treatment of patients with CU.

**Conflict of interest.** The authors declare no conflict of interest and no financial interest in the preparation of this article.

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### Особливості анестезіологічної допомоги хворим на холодову кропивницю (огляд літератури)

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**Резюме.** Холодова кропивниця (ХК) є алергічною реакцією, яка проявляється висипаннями за типом кропив'янки або червоних плям у відповідь на загальне або локальне охолодження тіла. Захворювання буває набутим або спадковим і в холодну пору року може уражувати всі верстви населення. Цей патологічний стан на перший погляд видається не дуже небезпечним варіантом локальної холодової травми, але в осіб, які схильні до впливу низьких температур, особливо з обтяженим холодним анамнезом, може супроводжуватися хронізацією процесу й ускладнюватися нейроваскулітом, облітеруючим ендартеріїтом і вторинним синдромом Рейно, може знизити якість життя постраждалих і стати причиною інвалідності. Патофізіологія ХК мало вивчена, але ймовірно пов'язана з імунoglobуліном E (IgE) та активацією тучних клітин. Охолодження тканин індукує викид хемотактичних факторів нейтрофілів та еозинофілів, простагландину D2 та фактора некрозу пухлин альфа (TNF- $\alpha$ ). Менш частою імунологічною знахідкою у пацієнтів з ХК є кріоглобулінемія з моноклональними IgG та змішаними IgG/IgM або IgG/IgA типами кріоглобулінів. Механізм розвитку ХК здебільшого визначається формуванням кріоглобулінів (холодних гемолізинів) та наступною дегрануляцією тучних клітин. Діагностика ХК залежить від анамнезу пацієнта та результатів холодних тестів. Пацієнтам з ХК рекомендують насамперед не переохолоджуватися, приймати теплий душ, носити теплий одяг та головний убір, не вживати холодну їжу та напої. Варіанти терапії включають H1-гістаміноблокатори другого покоління та глюкокортикоїди. Новою перспективною опцією є омалізумаб — моноклональне антитіло, яке отримується з рекомбінантної молекули ДНК і яке селективно зв'язує циркулюючий IgE і впливає на функцію тучних клітин. У пацієнтів з ХК, які підлягають загальній анестезії, в премедикацію рекомендовано включати антигістамінні та кортикостероїди, разом із суворим дотриманням періопераційної нормотермії.

**Ключові слова:** локальна холодова травма, холодова кропивниця, діагностика, лікування, анестезія