Obaidi *et al. Mil Med Res* 2026
https://doi.org/10.1016/j.mmr.2026.100007

MMR MILITARY MEDICAL RESEARCH

REVIEW Open Access

Frostbite: diagnosis, treatment, prognosis, and future directions

Noor Obaidi[1†], Olivia Agee[2†], Irene Yau[2], Robert Moritz[3] and Kristo Nuutila[3*]

Abstract

From cold-weather training to deployments in high altitude and arctic conditions, frostbite injury and its sequelae remain a serious concern in military operations. Frostbite harms tissue in two distinct ways. The first involves ice crystal formation within tissue, resulting in mechanical damage and ischemia. The second occurs secondary to the inflammatory and prothrombotic state caused by reperfusion from rewarming frozen tissue. Frostbite injuries can be classified in a number of ways, but no perfect system exists. Initial work-up and diagnosis are primarily clinical. However, in equipped treatment facilities, advanced imaging modalities such as technetium-99m (^{99m}Tc) bone scintigraphy, magnetic resonance angiography, single-photon emission computed tomography/computed tomography (SPECT/CT), and more can play a role in diagnosis and treatment. In resource-constrained environments, such as the deployed setting, management should involve an algorithmic approach. After concurrent hypothermia and/or trauma have been evaluated for and treated, active rewarming should take place so long as there is no risk of refreezing. During re-warming, surgical consultation and evacuation considerations should be considered. Once evacuated to a definitive treatment facility, thrombolytic as well as other therapies may be indicated. Unless there is evidence of severe damage or infection, surgical management is typically delayed until injury margins are fully demarcated. Longer-term prognosis is dependent on severity, with deeper injuries often resulting in longer hospital stays, more amputations, and chronic disability. Looking forward, future frostbite research should aim to bridge field and hospital care with the goal of minimizing tissue loss and accelerating functional recovery.

Key words Cold weather injury, Frostbite, Field care of frostbite, Military medicine

Background

Frostbite is a condition in which prolonged exposure to cold temperatures (below 0 °C/32 F) causes an injury resulting in tissue damage, starting superficially with the skin and potentially spreading deeper to blood vessels, muscles, tendons, and even bone [1]. Injury occurs when tissue cools, intracellular and extracellular ice crystals form. Further harm ensues with the inflammation and vessel coagulation that is associated with rewarming. Blisters and swelling are commonly seen following rewarming. Gangrene, where affected tissue withers and turns black, can also occur [2] (Fig. 1). Sometimes, even bones and tendons freeze. Thus, severe frostbite can result in severe injuries leading to significant morbidity and loss of function from distal extremity amputation [3,4]. Vulnerable populations include infants, young children, older adults, and patients with impaired circulation from conditions such as diabetes, who have reduced thermoregulatory efficiency [5]. Frostbite is also frequently observed among individuals experiencing homelessness and in those exposed to prolonged outdoor activities, such as mountaineering [6].

Frostbite remains a significant concern in military operations, particularly during cold-weather training or deployments in high-altitude and arctic environments. Military personnel are often exposed to extreme conditions for prolonged periods, increasing the risk of cold-induced injury [7]. Frostbite should be separated from non-freezing cold injury (NFCI), which is another class of local tissue damage caused by sustained exposure to low temperature. NFCI develops from prolonged exposure to cold above freezing, leading to vascular and nerve injury without actual tissue freezing. Frostbite typically causes rapid tissue damage, while NFCI develops gradually and often results in long-term neuropathic or circulatory sequelae, without causing rapid tissue damage like frostbite [8]. Clinical reports from military settings indicate that frostbite most often occurs during extended field exercises, static guard duty, and operations in

†Noor Obaidi and Olivia Agee contributed equally to this work
*Correspondence: Kristo Nuutila, kristo.j.nuutila.ctr@health.mil
[3]United States Army Institute of Surgical Research, Fort Sam Houston, TX 78234, USA
Full list of author information is available at the end of the article

Received: 24 September 2025 Accepted: 06 March 2026

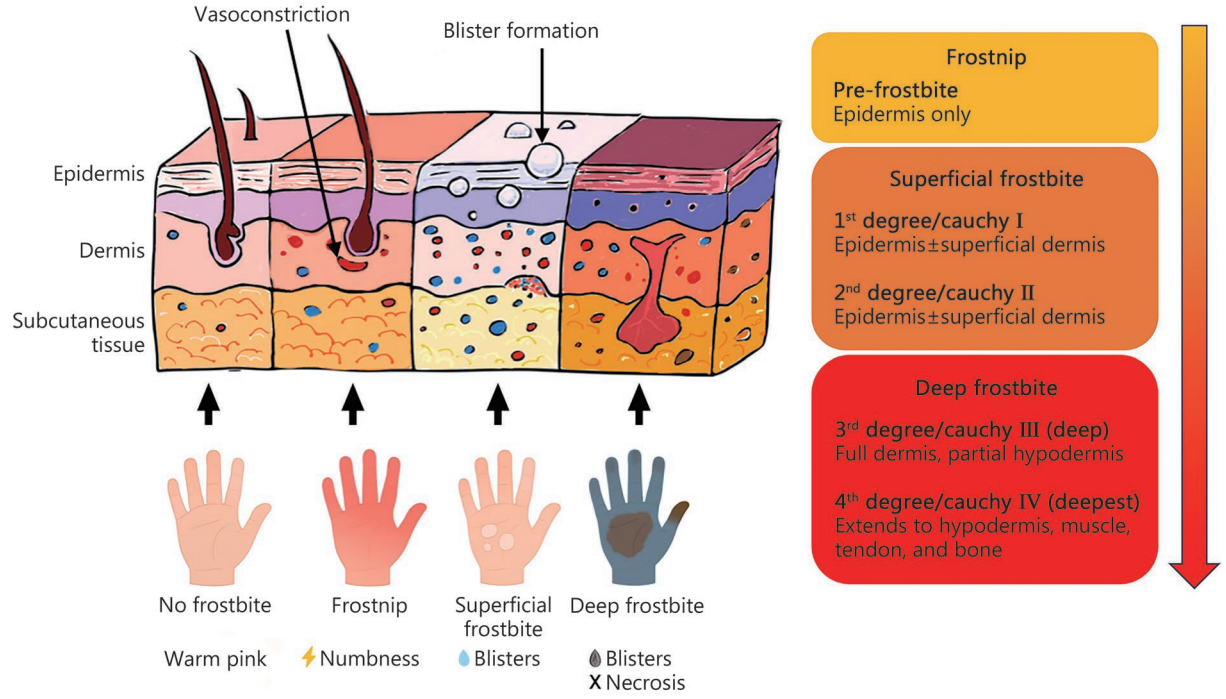

Fig. 1 The illustration on the left depicts changes in skin pathology and clinical appearance as frostbite severity increases. Frostnip (a mild form of cold injury) involves reversible vasoconstriction and numbness; superficial frostbite shows extracellular ice crystals and clear blister formation; deep frostbite demonstrates microvascular thrombosis, hemorrhagic blisters, and necrosis. Color coding indicates pathology: blue=vascular compromise, red=inflammation, black=necrosis. The panel on the right shows how frostnip, superficial frostbite, and deep frostbite correspond with the classification systems

mountainous or subzero climates. The toes, fingers, and ears are most commonly affected, with many cases progressing to full-thickness injury [9,10]. Outcomes are frequently worsened by delays in medical attention, particularly in austere or resource-limited environments. Military case series have reported high rates of digital amputations, persistent pain syndromes, and long-term neurovascular complications among affected personnel [11]. In addition, operational and logistical factors, such as the weight of cold-weather gear, restricted mobility, and the demands of mission-critical tasks, can limit both effective thermal protection and timely treatment [11]. These military-specific challenges underscore the importance of early recognition, rapid rewarming strategies, and the integration of robust frostbite prevention protocols into training and operational planning [12].

Approaches to treat and prevent cold-induced injuries have co-evolved alongside contemporary understanding of the underlying biology and physics of the environment. Limitations in scientific knowledge of the time applied to battlefield medicine have historically challenged operational readiness, tactical mobility, and the long-term health of soldiers. For example, Napoleon Bonaparte's Surgeon General, Dominique Jean Larrey, described slow rewarming of limbs as well as the rubbing of snow or ice on limbs. His frostbite treatment strategies were based upon an understanding of physiology at the time and continued to be applied for many years [13]. Such treatment guidance was followed in American military conflicts, including the Civil War, which documented 44 frostbite-related amputations. Cold, slow restoration of heat to injured limbs persisted as accepted treatment through World War I [14].

Studies demonstrating the advantages of rapid warming emerged during the 1930s in Russia, but western physicians were not aware until their translation in World War II [15,16]. The shift from slow, passive rewarming to rapid rewarming in warm water became one of the most important turning points in modern frostbite management. This change was driven primarily by laboratory and clinical research in the 1960s, particularly the work of Dr. William J. Mills [17], showing that rapid rewarming resulted in substantially better outcomes. Management of frostbite as a treatable hazard of winter warfare was tested within the global theatre of operation. The prospect of conflict in mountainous regions brought frostbite to the forefront of military medicine. Training exercises of the 10th Mountain Division in preparation for deployment to Italy in the Apennine Mountains recorded 195 cases of frostbite [18]. Impacts were felt not only in ground operations in austere terrain but also in flight operations. Missions carried out at

7600 m above sea level ranged from −30 to −43 °C. Among the 8th Air Force, the prevalence of high-altitude frostbite outweighed injuries incurred in actions against the enemy, with troops removed from duty for weeks at a time [19].

The American military within the modern era has benefitted from air superiority, robust medical support, and ongoing scientific advances, thus limiting the operational impacts of frostbite injury. A retrospective review of cold weather injury sustained during Operations Enduring Freedom and Iraqi Freedom found only two service members hospitalized for frostbite [20].

This review will detail advancements in the diagnosis and treatment of frostbite stemming from these historical lessons in the context of a modern military application. Additionally, this review will examine factors impacting prognostic outcomes of frostbite injury and areas where further development may occur.

Diagnosis

Pathophysiology

The pathophysiology of frostbite evolves through distinct but overlapping phases. In the prefreeze phase, vasoconstriction reduces peripheral blood flow to preserve core temperature, while increased blood viscosity and progressive tissue cooling contribute to numbness and pallor. During the freeze-thaw phase, ice crystal formation induces cellular dehydration and mechanical disruption, and subsequent rewarming triggers reperfusion injury through the generation of reactive oxygen species (ROS) and an inflammatory cascade characterized by edema and increased vascular permeability [21]. In the vascular stasis phase, endothelial injury promotes vascular leakage and microvascular thrombosis, resulting in impaired perfusion and progressive tissue hypoxia. In advanced cases, these processes culminate in the late ischemic phase, where irreversible necrosis and gangrene may occur, often necessitating amputation and carrying a risk of systemic infection [22].

Recent studies have expanded the understanding of frostbite pathophysiology by identifying key molecular and cellular mechanisms that drive tissue injury and repair. Cold-induced vasoconstriction and endothelial injury have been shown to initiate nitric oxide dysregulation, endothelin-1 upregulation, and activation of mitogen-activated protein kinase-driven inflammatory pathways, which increase inflammation, reduce blood flow, and worsen frostbite injury [23,24]. At the same time, tiny blood vessels clot (microvascular thrombosis) and tissues stop getting enough oxygen, causing severe hypoxia [25,26]. Low oxygen levels stimulate hypoxia-inducible factor-1α (HIF-1α) signaling that activates angiogenic, apoptotic, and metabolic responses, which try to repair damage and restore blood flow. However, in severe frostbite, this signaling can also contribute to cell death and tissue loss [27,28].

When keratinocytes are exposed to the extreme cold of frostbite and then rewarmed (freeze-thaw injury), several damaging changes occur inside the cells, including cytoskeletal disruption, mitochondrial dysfunction, and activation of stress-response pathways. Cytoskeletal disruption affects cell shape, stability, and movement, whereas mitochondrial dysfunction reduces energy supply and increases stress. Activation of stress-response pathways such as nuclear factor kappa-light-chain-enhancer of activated B cell, caspases, and β-catenin signaling triggers inflammation, drives apoptosis, and promotes tissue repair, respectively [29].

Furthermore, key proinflammatory cytokines, such as interleukin-1β and tumor necrosis factor-α, worsen endothelial injury by promoting inflammation and reducing blood flow [30]. During rewarming, growth factors, including vascular endothelial growth factor, platelet-derived growth factor, and transforming growth factor-β, facilitate keratinocyte migration and re-epithelialization. However, these regenerative processes are often impaired in deeper frostbite due to persistent ischemia and inflammation [30,31]. Together, these cellular and molecular insights highlight that frostbite recovery is an active, tightly regulated biological process. Building on this knowledge, molecular targets, such as modulation of β-catenin signaling, antioxidant pathways, and cytokine-directed therapies, may offer opportunities to improve frostbite outcomes.

Classifications

The diagnosis of frostbite is primarily clinical, based on careful examination of the affected area. Initial assessment includes visual inspection and palpation to evaluate skin color, temperature, and texture, as well as the presence of clinical signs such as erythema, pallor, blisters, or tissue induration. Symptom assessment is also essential, with attention to pain, numbness, tingling, and the degree of sensory and motor impairment [32]. These findings guide the classification of frostbite according to injury morphology, symptomatology, and pathophysiology outcomes [32]. Understanding different classification systems can help to guide prognosis and treatment strategies (Fig. 1 and Table 1).

Morphologically, frostbite has been categorized into four degrees of injury based on depth of injury, signs and symptoms, and predicted outcomes. This 4-degree classification system is primarily based upon findings during

Table 1 Summary of frostbite classifications

Frostbite category	Degree(s)	Signs & Symptoms	Tissue loss	Prognosis & Long-term effects	Key prognostic factors	Relevant imaging modalities & Purpose
Superficial frostbite	First & Second	First-degree: numbness, erythema, firm white/yellow plaques, mild edema, slight epidermal peeling; Second-degree: clear/milky blisters, surrounding erythema & edema	Minimal or none	Excellent; Full recovery expected; Rare cosmetic/functional impact	Timely treatment, quality of care, limited exposure, and good overall health	Infrared thermography - perfusion/temperature; Doppler ultrasound - vascular integrity
Deep frostbite	Third & Fourth	Third-degree: hemorrhagic blisters, injury extends into dermis & beneath vascular plexus; Fourth-degree: necrosis into subcutaneous tissue, muscle & bone; tissue hard, pale, anesthetic	Significant	Variable to poor; High amputation risk; Chronic pain, scarring, functional impairment	Timely surgical intervention, specialized care, severity/duration of exposure, and comorbidities	Technetium-^{99}m (^{99}mTc) bone scan - assess necrosis MRA, SPECT/CT - vascular/blood flow, tissue viability Conventional X-ray - bone involvement

MRA. Magnetic resonance angiography; SPECT/CT. Single photon emission computed tomography/computed tomography

and after rewarming. First-degree frostbite is superficial, presenting with reduced sensation, erythema, and burning after rewarming, and typically heals without sequelae. Second-degree frostbite involves the dermis, characterized by clear blisters and pain with rewarming, and may result in lasting cold sensitivity. Third-degree frostbite extends through the full thickness of the skin and presents with blue-gray discoloration and hemorrhagic or clear blisters. Fourth-degree frostbite involves deeper tissues such as muscle, tendon, and bone, and presents with blue-gray discoloration and insensate tissue after rewarming. Damage to growth plates may also occur in fourth-degree frostbite, which is associated with necrosis of underlying structures and a high risk of amputation [32,33] (Fig. 1 and Table 1).

The Cauchy classification of frostbite is based on early clinical findings observed after rewarming, including the presence and type of blisters, tissue color, and edema, and is used to predict the depth of injury and risk of tissue loss. It is divided into four grades: grade 1 involves erythema and mild edema with no blisters; grade 2 presents with clear blisters and partial skin necrosis; grade 3 features hemorrhagic blisters and deeper tissue involvement; and grade 4 represents full-thickness injury with a high risk of amputation [34].

The pathophysiological classification categorizes frostbite according to the underlying tissue damage mechanisms. As depicted in Fig. 1, superficial frostbite affects only the epidermis and possibly the superficial dermis, with largely reversible injury, whereas deep frostbite involves full-thickness skin, subcutaneous tissue, and sometimes underlying muscle, tendon, or bone, often associated with vascular thrombosis and a higher risk of tissue loss [35] (Fig. 1 and Table 1).

Imaging modalities

One of the major challenges in managing frostbite is accurately assessing the depth and extent of tissue injury while preserving as much limb length as possible. Amputation is often required for cases of deep tissue necrosis; however, traditionally, it can be delayed for weeks to months until full tissue demarcation is apparent [36]. Recent advances in imaging have created opportunities to guide earlier surgical decision-making, potentially improving salvage and functional outcomes. Techniques such as technetium-99m (^{99m}Tc) bone scintigraphy, magnetic resonance angiography (MRA), and single-photon emission computed tomography/computed tomography (SPECT/CT) provide functional and anatomical insights to identify necrosis and inform debridement or amputation timing [36]. Radiography detects severe bone involvement, Laser Doppler imaging (LDI) assesses vascular patency, and

infrared thermography non-invasively identifies perfusion deficits [37]. Utilization of these tools improves diagnostic accuracy, surgical planning, and outcomes, as described in the paragraphs below.

Bone scintigraphy with ^{99m}Tc is used to assess blood flow and bone viability, and integration with SPECT/CT enhances spatial localization. A retrospective study of 92 severe frostbite cases demonstrated that ^{99m}Tc scintigraphy accurately delineated zones of perfusion loss, helping in the prediction of eventual amputation and enhancing the classification of injury severity [38]. Another study employing SPECT/CT imaging confirmed that this technique not only improved the localization of viable vs. non-viable tissue but also provided additional prognostic information, allowing for earlier decision-making about surgical intervention [39].

Conventional catheter-based angiography visualizes arterial flow in real time, detecting occlusions or delayed perfusion in frostbitten extremities. In a clinical series of 62 patients, angiographic assessment was paired with intra-arterial thrombolytic therapy, showing that targeted reperfusion significantly reduced amputation rates compared with historical controls [40]. Additional studies reinforced these findings, demonstrating that thrombolytic treatment guided by angiographic perfusion mapping salvaged digits that otherwise would have progressed to necrosis [41,42]. More recently, a protocolized approach incorporating angiography with adjunctive iloprost demonstrated improved phalangeal salvage rates and functional recovery, suggesting standardized, imaging-guided reperfusion protocols may optimize outcomes [43].

Magnetic resonance imaging (MRI) and MRA provide detailed soft-tissue and vascular imaging without radiation exposure. A case report demonstrated that MRI can define the depth of frostbite injury, visualizing edema, necrosis, and microvascular disruption noninvasively. Although not widely used, MRI offered superior delineation of viable versus necrotic tissue compared with clinical examination, suggesting a role in selected cases where surgical decision-making is complex [44].

Indocyanine Green Fluorescence Angiography (ICG-FA)/Fluorescence Microangiography (FMA)-based imaging uses a fluorescent dye that binds plasma proteins and emits near-infrared light, allowing real-time visualization of tissue perfusion at the bedside. An emergency department case report showed that fluorescence microangiography could immediately detect areas with compromised flow in frostbitten digits, correlating well with eventual tissue outcomes [45]. Similarly, other studies have demonstrated that ICG-FA can predict which tissues would recover or progress to necrosis, aiding early decisions about thrombolytic therapy and surgical planning. These findings correlate with clinical salvage rates, making ICG-FA/FMA a promising point-of-care adjunct [46,47].

LDI measures cutaneous microcirculatory perfusion using Doppler-shifted laser light, generating high-resolution perfusion maps. A clinical case report demonstrated that LDI identified areas of severely reduced blood flow in frostbite injury earlier than visible skin changes appeared [48]. These perfusion maps helped predict which tissues were likely to be salvageable, highlighting the value of LDI as a noninvasive tool for early prognosis in frostbite patients [48].

Thermal imaging detects infrared radiation from the skin surface to assess temperature and perfusion. In a rabbit frostbite model, thermography accurately distinguished viable from non-viable tissue, supporting its diagnostic potential [49]. Clinically, thermography and Dynamic Infrared Thermography with rewarming tests have been used to monitor microvascular recovery, demonstrating a noninvasive ability to identify ischemic areas at risk for necrosis and to complement clinical staging of frostbite injuries [50].

Management

Recommendations on prevention as well as field and definitive management of frostbite injuries are discussed in the subsequent paragraphs. Frostbite avoidance strategies are touched upon because injury prevention reduces suffering and minimizes healthcare costs. Next, a general algorithmic approach to field treatment is provided based upon current military treatment guidelines and additional considerations (Fig. 2). Finally, definitive management, including thrombolytic therapy and surgical intervention, is discussed. Although this section is framed around the management of frostbite in soldiers, the treatment phases and pharmacologic interventions it describes are equally applicable to civilian practice.

Prevention

Prevention measures involve minimizing risks from the two broad categories of environmental and personal health-related factors. Reducing environmental risk factors includes minimizing cold exposure duration, appropriate use of cold weather gear, avoidance of wet extremities or constrictive clothing, and use of supplemental oxygen in severely hypoxic conditions, such as at altitudes greater than 7500 m [51]. Health prevention measures include ensuring adequate hydration and nutrition, as well as avoidance of substances that can impair perfusion, such as tobacco products. Additionally, "numbness" can serve as a harbinger of frostbite, so self-checks or medic inspections should regularly be performed when

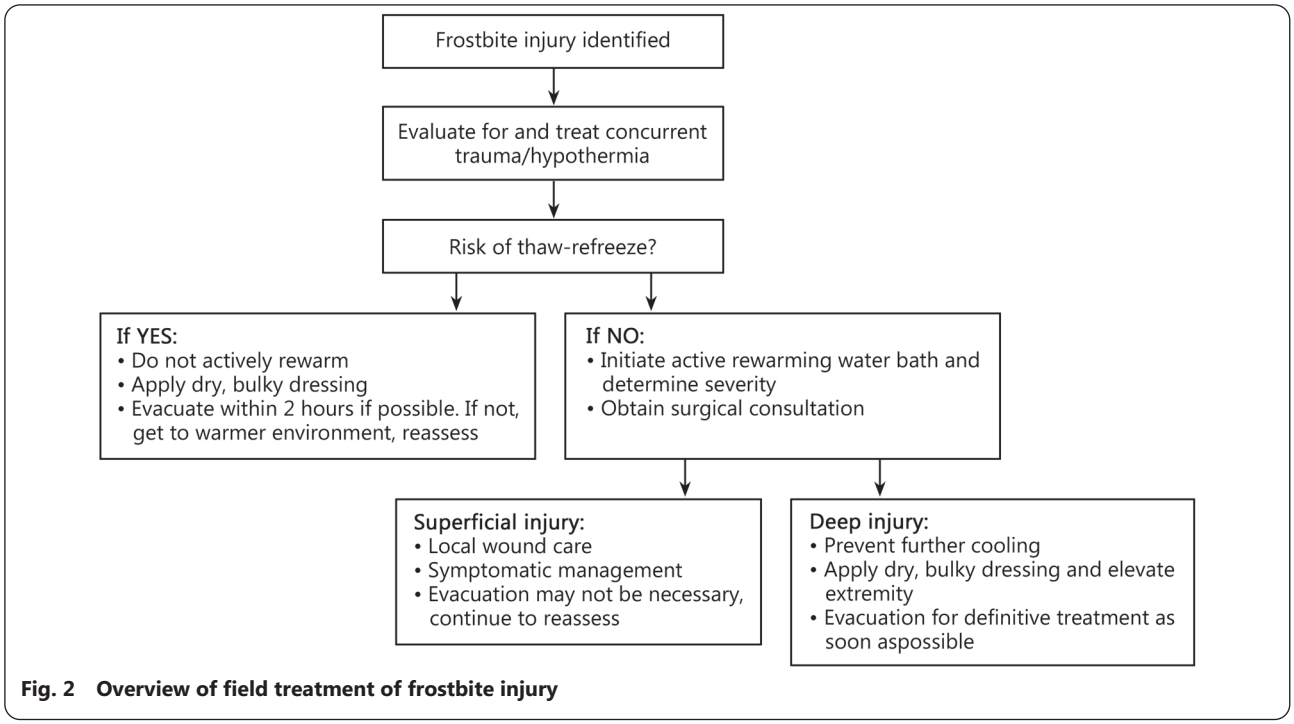

Fig. 2 Overview of field treatment of frostbite injury

operating in cold environments [51,52].

Field treatment of frostbite

Despite prevention efforts, frostbite injury can still occur. The first step in field treatment of a soldier with a suspected frostbite injury is to evaluate them for the presence of hypothermia and/or other life-threatening injuries, such as concurrent trauma. These conditions must be treated first [52]. This trauma evaluation should occur in a warmer environment, if possible, and any wet or constricting articles of clothing or jewelry should be removed [53].

Once the above evaluation is complete, the risk for refreezing needs to be assessed before initiating rewarming of the affected extremity. This decision point is crucial in the field treatment process as thawing and refreezing lead to the greatest tissue damage and worse outcomes [54]. If there is risk of refreezing, the extremity should remain frozen, if possible, and no active rewarming should take place [51,52,54]. Depending on the operational environment, risk-benefit analysis may be needed when weighing the potential to exacerbate tissue injury from ambulation on a frozen extremity [51]. For both ambulation and evacuation, the patient's extremity should be padded, splinted, bandaged with dry dressings, and protected from any heat sources that would slowly rewarm the extremity [51,52].

If there is no risk of refreezing, the standard is to initiate treatment with rapid rewarming. Rapid rewarming helps to restore tissue perfusion, and the use of a water bath is the preferred method [52,53]. The extremity should be immersed in a bath of gently circulating water at 40–42 °C. Extremities should remain immersed until they become flushed, soft, and pliable, with the typical timeframe of 15–30 min. Warm water should be replenished as needed during the process. A thermometer should be utilized as reduced effect is seen with cooler bath temperatures, and burns can be seen in cases of hotter temperatures [52-54]. If a thermometer is not available, the caregiver can place their hand in the water for at least 30 s to determine an adequate temperature that will not burn the patient [51].

Due to the severe pain associated with the rewarming process, use of a non-steroidal multimodal pain regimen including non-steroidal anti-Inflammatory drugs (NSAIDs), narcotics, and/or ketamine is recommended. If possible, electrolytes should be monitored every 6 h until normalization due to the risk of electrolyte abnormalities and rhabdomyolysis [52]. Consideration of the evacuation of the soldier should occur concurrently with the above rewarming process. Although operative interventions are typically performed at more definitive treatment facilities, surgical consultation should be obtained as early as possible in the field [53].

The standard treatment, a warm water bath, is a form of active rewarming. Dry heating is not considered an acceptable alternative, although it may be the only viable option in austere conditions [51,53]. In general, rewarming over an open fire or high heat source should be avoided. Rubbing or massaging of impacted tissue should be avoided, as this could exacerbate tissue damage [51,53]. Additionally, vasoconstrictive medications for

the use of tobacco or nicotine-containing substances should be avoided. Tetanus booster should be administered based on immunization status. Photo documentation at the point of injury and after rewarming should be obtained, if possible [53].

Following rewarming, further field management is dependent on clinical judgement on the severity or estimated depth of tissue involvement. Because many frostbite injuries have a similar clinical appearance upon initial presentation, severity cannot be assessed until after the above-described rewarming process is complete. Even following rewarming, the extent of injury is often not truly known until several weeks or even months later [54,55].

Definitive management

As previously mentioned, the four-degree classification of frostbite occurs retrospectively and is not fully known until well after field rewarming has completed [56]. Thus, determining whether the injuries are superficial or deep may be more clinically useful. First and second encompass superficial injury, and third and fourth degree likewise fall under deep injury. Notably, superficial injuries may also be found surrounding deeper injuries [57]. The subsequent paragraphs dive into greater detail of field treatment of superficial and deep injuries, as well as management guidelines at a more definitive facility [54,57].

Superficial injuries are less severe by definition and may not necessitate evacuation if there is no full-thickness involvement. These injuries can be treated with supportive wound care and symptom management. Local wound care typically involves twice daily changes of sterile nonadherent dressings and application of topical emollients every 6 h [52,54]. Soldiers may complain of persistent pain and hyperhidrosis and can usually be managed with NSAIDs and antiperspirants, respectively [52]. Deep injuries, on the contrary, should be evacuated for definitive treatment as soon as the operational environment allows. In the meantime, affected extremities should be dressed with a dry, sterile bandage, elevated, and protected from refreezing before and during evacuation [54].

Thrombolytic therapy and other post-rewarming treatment measures should be considered when a more definitive treatment facility is reached [52,53]. Tissue plasminogen activator (tPA) can be utilized in frostbite management, with the rationale for use being the drug's ability to lyse microvascular thrombi [58]. Administration of tPA may be indicated if the following two criteria are met: the patient is within 24 h since frostbite injury onset, and they display evidence of vascular compromise [52,53]. Findings suggestive of circulatory compromise include decreased or absent pulses or Doppler signals, delayed capillary refill, and/or ischemic discoloration. Thrombolytic therapy is contraindicated if greater than 48 h have elapsed or if there is evidence of freeze-thaw-freeze injury or in cases of bleeding risk, such as in the setting of concurrent trauma, hemorrhage, bleeding disorders, or recent surgery [52,53].

The current Joint Trauma System (JTS) Clinical Practice Guidelines (CPG) recommendations for intra-arterial thrombolytic therapy are primarily based upon the findings from the 2007 and 2016 retrospective reviews conducted by Bruen *et al*. [40] and Gonzaga *et al*. [59], respectively. Both studies found that the timely administration of tPA resulted in improved perfusion and decreased amputations. The JTS CPG recommends a diagnostic arteriogram to assess for impaired perfusion in the tPA candidates. If perfusion is limited on arteriogram, a vasodilator, such as papaverine, can be administered intra-arterially to decrease local vasospasm [52,59].

Regarding specific tPA dosing, a 2–4 mg bolus should be followed by continuous infusion at a rate of 0.5–1.0 mg/h via intra-arterial brachial or femoral catheter sheath. In cases of bilateral extremity involvement, a rate of 0.5 mg/h in each catheter is recommended so that the total dose of 1 mg per hour is not exceeded. Intra-arterial heparin should also be initiated simultaneously at a rate of 500 U/h to prevent clot formation or further propagation. During tPA administration, diagnostic arteriograms should be obtained every 8–12 h to assess for perfusion improvement [52]. Serial labs of partial thromboplastin time (PTT), fibrinogen, hemoglobin/hematocrit, and platelets should be obtained every 6 h. If fibrinogen levels fall below 150 mg/dl, tPA infusion should be discontinued. Thrombolytic therapy should also be stopped after 48 h of treatment or sooner if complications arise or complete perfusion is achieved. In such cases of revascularization, heparin should be continued for at least 72 h following cessation of tPA [40,52,59].

Systemic intravenous administration of thrombolytic therapy exists as an alternative for candidates, so long as the military treatment facility is equipped with Tc scanning to confirm impaired perfusion and assess treatment response [52]. The systemic dosing consists of a tPA bolus of 0.15 mg/kg intravenously followed by a continuous rate of 0.15 mg/(kg·h) up to a total dose of 100 mg over 4–6 h. Immediately following completion of intravenous, therapeutic heparin should be initiated for 3–5 d. Patients should then be transitioned to warfarin, which is continued for a 4-week duration [52,60].

Based upon their 2024 clinical practice guidelines from systematic literature evaluation, the American Burn Association (ABA) recommendations parallel aspects of

the above-mentioned JTS guidelines [52,61]. For example, ABA also recommends early administration of thrombolytic therapy, but preferably within 12 h rather than 24 h. They also note that intra-arterial and intravenous routes of tPA delivery exist as options and do not recommend one over the other. The ABA differed, however, in that they were unable to provide recommendations for the use of vascular imaging studies, including angiography and scintigraphy, to guide initiation or administration of thrombolytic therapy. Authors discussed potential downsides of obtaining imaging before treatment, such as the risk of reaction to the dye and the risk of extending warm ischemia time and delaying definitive treatment [61]. Of note, ABA's conclusion that no formal recommendations can be made is based upon only two low-quality retrospective studies that were found to be pertinent. Ultimately, clinical judgement should be used in deciding whether or not to obtain imaging before thrombolytic therapy, especially in soldiers who present several hours following injury [61].

Iloprost is an additional treatment measure to consider. Previously unavailable in the United States, the Food and Drug Administration (FDA) approved the use of intravenous iloprost for the treatment of severe frostbite to reduce amputation risk in February 2024 [62,63]. The drug is a prostaglandin analog that demonstrates several vascular-related functions, such as promoting vasodilation and inhibiting platelet activation [64]. Because of the vasoconstriction and microthrombosis that occur in frostbite injury, iloprost serves as a reasonable treatment option [65]. In Cauchy *et al*.'s [66] letter to the editor, the authors remarked on the drug's efficacy following their randomized study with 47 adults with severe frostbite. They found that patients treated with aspirin plus iloprost had a statistically significantly lower amputation rate of 0% compared with the other two treatment groups of aspirin plus buflomedil and aspirin plus iloprost plus fibrinolysis with rates of 60% and 19%, respectively. Additional case reports are also supportive of the benefit of iloprost in severe frostbite treatment [65,67,68]. One additional caveat is that there is not a plethora of high-quality evidence supporting iloprost use, as the available sources consist of a single 47-patient study and observational reports. Some practice guidelines, including US military guidelines, do not yet recommend vasodilators, as they were written prior to FDA approval [52,61,69].

Other inpatient treatment measures to consider in addition to thrombolytic therapy include symptomatic management, wound care, hydrotherapy, hyperbaric oxygen therapy, physical therapy, and operative intervention [52,53]. A nonsteroidal multimodal pain regimen is recommended while inpatient, with narcotics reserved for severe breakthrough pain, as pain typically subsides after 3 d. Scheduled NSAIDs, such as ibuprofen, can help to inhibit harmful prostaglandins and should be initiated in the field and continued until the frostbite wound is healed or surgery is performed. Ibuprofen can be less harmful to the gastrointestinal tract and is recommended to be taken at 400 mg every 6 h by mouth [52,53,69].

Daily wound care for thawed extremities should be performed while inpatient, as blisters and vesicles may form following rewarming. Blisters that are hemorrhagic in appearance should be left intact. Dressing changes for unroofed blisters primarily consist of loose, dry, sterile dressing wrappings with digits gently separated to prevent friction and further damage [54,69,70]. Additionally, topical application of aloe vera before dressing may help to limit tissue loss via reduction of prostaglandin and thromboxane formation based on observational animal models [61]. Other topical anti-inflammatory agents may work in theory, but no literature was found studying or recommending gels or solutions other than aloe vera.

Once to twice daily hydrotherapy, or whirlpool therapy, can also be considered following resolution of edema [52,54,69]. Hyperbaric oxygen therapy may have some benefit in the treatment of frostbite injury, but data are limited [69]. If used, JTS CPG recommends starting 5–10 d after injury [40]. Providers should also consider physical therapy evaluation and treatment, particularly for help with joint mobility. Additionally, routine antimicrobials are not recommended [61,71].

Although surgical consultation should be initiated as early as possible, surgery should not be performed in the operational environment when there is the ability to evacuate patients. Unlike burns, early excision of tissue is not typically part of the treatment algorithm for frostbite. In some cases, operative intervention in the acute setting is necessary. If there are signs of concurrent infection or wet gangrene, surgical management with debridement or possible amputation should be conducted expediently for source control [72,73]. Additionally, fasciotomy should be performed in the acute setting if compartment syndrome develops from edema in the immediate period following thawing of tissue [73]. Early surgery may also be indicated in cases of severe tissue destruction, as seen in the thaw-refreeze course [52,54].

Soft tissue debridement usually takes place after injury margins are fully demarcated, which sometimes occurs several weeks later. Patients may even be discharged with a plan for readmission for definitive surgical management [72]. For tissue coverage and function restoration following debridement, skin grafts, local, and free flaps can be utilized. Such flaps and additional reconstructive interventions, including digit

transposition, may be necessary depending on the injury location on the hand or foot [70]. Again, reconstructive measures are typically delayed, often taking place several weeks following injury.

Prognosis

The predicted course following frostbite injury is dependent on the severity of tissue involvement. This section will discuss the clinical recovery timeline, complications, and factors influencing the prognosis of frostbite injuries.

As mentioned previously, pain during rewarming of superficial injuries is expected to be transient and mild. In the first few days following rewarming, common findings include edema, vesicle formation, and hyperhidrosis with associated desquamation around 5 d later. Sensation will be intact, and pain is expected to improve after 3 d, but throbbing, shooting, burning pain may occur and can persist over several weeks [57]. Vesicles seen in second-degree frostbite typically become dry, black, and hard 2 weeks after onset and generally peel away at 3–4 weeks. Overall, if appropriate care is received and the dermis is spared, healing is common, and prognosis is excellent [56].

Compared with superficial injuries, the clinical course of deeper injuries typically includes longer hospital stays, greater tissue loss, and chronic disability. More severe pain upon rewarming is expected with deeper injuries, and findings after rewarming can include edema, cyanosis, blister formation, and soft, boggy, non-blanchable skin appearance that can also be mottled [74]. The edema of proximally involved areas will later demarcate between viable tissue and full-thickness injuries [56]. Blisters can be left in place and are expected to slough off 7–10 d later. Some blisters may rupture and can be treated with the wound care mentioned previously [5]. In cases of deeper injury, eschars may become apparent and subsequently debrided at 2–8 weeks post-onset. Mummification of extremities or digits becomes apparent around two weeks post-injury. Throbbing, shooting pains, and aching can be expected during mummification, but it is otherwise minimally painful. Neuropathic pain can be seen following amputation or mummification of digits [56].

The average hospital stay for frostbite in the United States is estimated to be 9 d [54,72]. Longer hospitalization or unplanned readmissions can also occur due to frostbite-related complications, such as nonhealing wounds, osteonecrosis, and infection, such as cellulitis or osteomyelitis [72]. The average hospital stay in such readmissions was found to be 34.7 d, but patients also had several socio-economic factors that would place them at higher risk of readmission compared to an active-duty soldier [72]. Regarding long-term sequela, neuropathy can be associated with both superficial and deep frostbite injuries. Specific examples include chronic dysesthesia, chronic pain, hyperhidrosis, vasospasm, and decreased nerve conduction velocity [4]. Other sequelae include contractures, increased cold sensitivity, chronic ulceration, and arthritis, which present similarly to osteoarthritis [4,5].

Overall factors or findings that can lead to more severe injuries include harsher environmental conditions, health status at the time of injury, prolonged time until rewarming, thaw refreeze course, frankly frozen tissue upon initial presentation, and certain physical exam findings following rewarming [34,54,56,75]. Environmental conditions that predispose injury include lower absolute temperatures, higher altitudes, longer exposure time, wind chill, and increased humidity [55,76]. Health aspects that increase risk of frostbite and may prolong recovery include preceding dehydration or malnutrition, prior history of frostbite injury, tobacco use, alteration due to poor mental health or intoxication state contributing to prolonged exposure, and pre-existing state of or abnormal peripheral circulation [53,58]. Prolonged time before rewarming can lead to greater amputation risk, but the thaw-refreeze course leads to multiple cycles of tissue injury and is related to worse outcomes [4,52,77]

The presence of the following after field rewarming is indicative poorer prognosis: skin remains cool, digit numbness or lack of pain upon rewarming, cyanosis, or hemorrhagic blisters [70]. Although the superficial vs. deep clinic classification system can be more clinically relevant than the four-degree system, such early clinical assessments seem to have poor prognostic utility on tissue viability [55,56]. The frostbite classification scheme proposed by Cauchy *et al*. [34] may have better prognostic value, as it notes that more proximal cyanosis, including the presence of hemorrhagic blisters, correlated with a higher amputation rate. Although it has not been prospectively validated, several civilian pre-hospital frostbite protocols utilize the Cauchy *et al*. [34] grading system [51,53,55].

Future directions

Over the last 10 years, therapeutic advances have been made with the early use of fibrinolytic agents, such as tPA, to reduce the incidence and morbidity associated with distal extremity tissue loss [78,79]. The vasodilator drug iloprost has been used with some success, as described earlier [80,81]. The use of other vasodilators such as buflomedil (since withdrawn from the market) and reserpine has been explored in the management of frostbite, but supporting clinical data are very limited and of low quality [82]. Pentoxifylline, a

hemorheologic agent that improves blood flow by decreasing blood viscosity and increasing red blood cell flexibility, has shown some promise as an adjunctive therapy in animal studies and human observational reports [83]. However, large, controlled, randomized trials demonstrating clear efficacy are still lacking. Additionally, off-label administration of botulinum toxin has emerged as a potential therapeutic approach for patients with frostbite sequelae, with reported benefits including improved peripheral blood flow and reduced cold sensitivity and neuropathic pain [84]. Furthermore, non-pharmacologic adjunctive treatments such as hyperbaric oxygen therapy (HBOT) and nerve blocks have been proposed. HBOT may improve healing outcomes by enhancing oxygen delivery to damaged tissues and reducing edema. In frostbite management, HBOT involves breathing 100% oxygen at increased pressure in a hyperbaric chamber, with optimal timing occurring early in the rewarming process [85]. While HBOT shows promise, more research is needed, as most available evidence comes from animal studies and small clinical series.

However, all these interventions have significant limitations. They are administered systemically over several days, which is not feasible in austere environments. Systemic administration frequently fails to achieve therapeutic drug concentrations in frostbite-affected tissues owing to impaired microcirculation [78]. Furthermore, prolonged systemic use may induce adverse side effects, thereby restricting its applicability in remote or resource-limited environments [86]. Surgical interventions, typically reserved for severe cases, are delayed until tissue demarcation is complete, thereby prolonging recovery and increasing the risk of infection [79]. Consequently, a localized, sustained drug delivery platform capable of providing high therapeutic concentrations directly to the affected area while minimizing systemic side effects, particularly in field care or en route settings, would be advantageous in the management of frostbite.

Research is essential to advance both the scientific understanding and clinical care of frostbite, and the development of robust, reproducible animal models is key to this effort. A well-designed model that allows precise quantification of tissue histology, healing dynamics, and tissue loss following frostbite could significantly accelerate research and drive innovation in both prevention and treatment strategies. Such models would also provide a rigorous framework for evaluating the efficacy of existing interventions, ensuring that clinical practices are grounded in solid evidence [87]. Moreover, by enabling detailed investigation of underlying pathophysiological mechanisms, such as apoptosis, microvascular injury, and the role of ROS, preclinical models can help identify novel therapeutic targets and inform the rational design of future therapies [88,89].

Although several animal models of frostbite have been developed, relatively few are well-established and clinically relevant [90]. Auerbach *et al.* [91] developed a mouse model designed to quantify affected skin surface area, histology, healing rate, and skin loss. In this model, frostbite injuries were induced by applying frozen magnets (–78.5 °C) to the dorsal skin, either as a continuous 5-minute freeze or as three repeated cycles of 1-minute freezing followed by 3-minute thawing. The authors were able to demonstrate full-thickness skin necrosis, inflammation, and healing with neovascularization. Ummadisetty *et al.* [92] induced frostbite in the hind paws of rats by using a –20 °C deep-freeze magnet. They performed various behavioral assays and demonstrated that frostbite injury exhibited significant mechanical, thermal, and cold hypersensitivity in rats. Junila *et al.* [93] developed a rabbit ear model of frostbite injuries. Frostbite was induced using a liquid nitrogen-cooled glass bottle, and thermography was used to track thermal changes over time. Initially, the frostbitten area appeared warmer than the surrounding tissue, progressing to diffuse cold spots at one week and a well-demarcated cold area by three weeks. Furthermore, Schoning *et al.* [94] produced frostbite lesions in Hanford miniature swine by exposing them to –75 °C air for varying durations. Serial biopsies over two weeks revealed a progression of microscopic changes: early keratinocyte vacuolation, pyknosis, and cell individualization; intermediate degeneration and microabscess formation; and late necrosis and epithelial regeneration. Similarly, Rothenberger *et al.* [95] used Göttingen minipigs to develop a reproducible platform for studying frostbite pathophysiology. In their model, frostbite injuries were inflicted on the abdomen using an aluminum frozen with liquid nitrogen to –196 °C.

A limitation of many frostbite models, particularly in large animals, is that injuries are often induced on the dorsum or abdomen, whereas frostbite in humans typically affects the toes, fingers, ears, nose, and other extremities. Although porcine skin closely resembles human skin, models with dorsal frostbite do not fully replicate the clinical scenario. Another limitation of current models is that frostbite is typically induced through direct contact with extreme cold, similar to contact burns, whereas in real life, frostbite develops gradually over time.

Accurate diagnostics are important and will help providers make decisions when planning treatment. Therefore, integration of artificial intelligence (AI) into clinical decision-making could play an important role in the future management

of frostbite. AI systems have already been applied to improve diagnostic precision, risk stratification, and treatment planning across multiple fields, including radiology, oncology, neurology, and critical care [96]. A recently published study introduced an AI-based system for classifying thermal burn depth using multimodal imaging (digital photographs and ultrasound tissue doppler imaging) integrated within an electronic medical record framework. The system was able to distinguish first-, second-, and third-degree burns with 84% accuracy [97]. Because imaging modalities such as SPECT/CT are commonly used for frostbite diagnostics and surgical planning, AI integration could further enhance accuracy and ultimately improve healing outcomes.

Limitations

This article has limitations worth noting. First, the supporting literature is primarily retrospective studies and case reports. Such studies can be subject to missing data, selection bias, confounding variables, and lack of generalizability in the case of small sample observational reports. The field lacks randomized controlled trials, which impairs the strength of clinical recommendations. Second, this article does not employ a formal evidence grading system to assess the quality of the studies cited. Regarding field treatment recommendations, the article primarily relies on information from the most current JTS CPG and Emergency War Surgery book, which are a mix of evidence and expert opinion based on [52,54]. Utilizing these sources from 2017 and 2018, respectively, is limited in that they may not be the most up-to-date with civilian equivalent guidelines. Regarding management recommendations, the two military sources above are referenced in addition to other literary sources, including civilian guidelines, retrospective studies, and observational studies. Use of a grading system to assess the quality of evidence for the variety of source types mentioned would likely help to improve clinical decision-making, and is once again a limitation of this article.

Conclusions

Frostbite results from prolonged cold exposure, leading to tissue injury. It remains a significant concern in military operations, particularly during cold-weather training or high-altitude deployments [5]. Management begins with accurate diagnosis: although imaging modalities such as radiography, MRI, and bone scintigraphy can provide additional insight in select cases, clinical examination remains the primary method for assessing injury and guiding classification. After rapid thawing, pharmacologic interventions are employed to enhance circulation. Early tissue excision is avoided, and surgical management, when necessary, typically involves delayed amputations [98,99].

The future of frostbite management lies in early, precise diagnosis, targeted pharmacologic and regenerative therapies, and technologies that bridge field and hospital care, with the ultimate goal of maximizing tissue salvage, minimizing amputations, and accelerating functional recovery. Achieving this will require research using relevant preclinical models.

Abbreviations

ABA: American burn association
AI: Artificial intelligence
CPG: Clinical practice guidelines
FDA: Food and Drug Administration
HBOT: Hyperbaric oxygen therapy
ICG-FA: Indocyanine green fluorescence angiography
JTS: Joint trauma system
LDI: Laser doppler imaging
MRI: Magnetic resonance imaging
NFCI: Non-freezing cold injury
NSAIDs: Non-steroidal anti-inflammatory drug
ROS: Reactive oxygen species
SPECT/CT: Single-photon emission computed tomography/computed tomograph
tPA: Tissue plasminogen activator

Acknowledgement

Not applicable.

Authors' contributions

All authors contributed to the writing of the manuscript, reviewed, commented, and edited the final version. NO, OA, and KN prepared the figures and tables. All authors read and approved the final version of the manuscript.

Funding

Not applicable.

Availability of data and materials

Not applicable.

Declarations

Ethics approval and consent to participate

Not applicable.

Consent for publication

Not applicable.

Competing interests

The views expressed in this article are those of the authors and do not reflect the official policy or position of the U.S. Army Medical Department, Department of the Army, DOD, or the U.S. Government. The authors declare that they have no conflicts of interest.

Author details

[1]The Metis Foundation, San Antonio, TX, 78216, USA. [2]General Surgery,

William Beaumont Army Medical Center, Fort Bliss, TX 79906, USA. [3]United States Army Institute of Surgical Research, Fort Sam Houston, TX 78234, USA.

References

1. Kowtoniuk RA, Liu YE, Jeter JP. Cutaneous cold weather injuries in the US military. Cutis. 2021;108(4):181-184.
2. Norheim AJ, Sullivan-Kwantes W, Steinberg T, Castellani J, Friedl KE. The classification of freezing cold injuries - a NATO research task group position paper. Int J Circumpolar Health. 2023;82(1): 2203923.
3. Lindford A, Valtonen J, Hult M, Kavola H, Lappalainen K, Lassila R, *et al*. The evolution of the Helsinki frostbite management protocol. Burns. 2017;43(7):1455-63.
4. Regli IB, Strapazzon G, Falla M, Oberhammer R, Brugger H. Long-term sequelae of frostbite – a scoping review. Int J Environ Res Public Health. 2021;18(18):9655.
5. Basit H, Wallen TJ, Dudley C. Frostbite. In: StatPearl. Treasure Island (FL): StatPearls Publishing; 2025. https://www.ncbi.nlm.nih.gov/books/NBK536914/.
6. Endorf FW, Nygaard RM. Social determinants of poor outcomes following frostbite injury: a study of the National Inpatient Sample. J Burn Care Res. 2021;42(6):1261-5.
7. van Dongen TTCF, Berendsen RR, de Jong FJM, Endert EL, van Hulst RA, Hoencamp R. Frostbite: a systematic review on freezing cold injuries in a military environment. BMJ Mil Health. 2025;171(1):81-85.
8. Zafren K. Nonfreezing cold injury (trench foot). Int J Environ Res Public Health. 2021;18(19):10482.
9. Lorentzen AK, Penninga L. Frostbite – a case series from Arctic Greenland. Wilderness Environ Med. 2018;29(3):392-400.
10. Schissel DJ, Barney DL, Keller R. Cold weather injuries in an arctic environment. Mil Med. 1998;163(8):568-71.
11. Powell T. Development of second-degree frostbite in two service members wearing issued cold weather footgear traversing sea ice. Mil Med. 2021;186(11-12):e1250-e1253.
12. Klous L, Teien H, Hollis S, Levels K, Boonstra A, Sullivan-Kwantes W, *et al*. Cold weather operations: preventive strategies in a military context. Temperature (Austin). 2024;12(1):8-27.
13. Larrey DJ. Memoirs of military surgery, Vol. II. 1814:156. https://archive.org/details/2561003RX2.nlm.nih.gov. Accessed Jan 20, 2026.
14. Medical and Surgical History of the War of the Rebellion. Washington: Government Printing Office; 1883. pt. III, vol. II, pp. 670-679, passim.
15. Ariev TJ. Monograph on frostbite: pathological anatomy, pathological physiology, pathogenesis, clinical considerations, prophylaxis, and treatment. 1955.
16. Sokolov V, Biryukov A, Chmyrev I, Tarasenko M, Kabanov P. Burns and frostbite in the Red Army during World War II. Mil Med Res. 2017;4:5.
17. Gharraei M, Zafren K, Villar R, Giesbrecht GG. Keep cool but don't freeze: the influence of William J. Mills Jr. on the treatment of frostbite. Wilderness Environ Med. 2024;35(4):496-505.
18. Whitlock F, Miller E. 10th mountain division at camp hale. Arcadia Publishing; 2023.
19. Monthly Progress Report, Army Service Forces, War Department. 31 Aug 1944, Section 7: Health. https://archive.org/details/22310600RX17.nlm.nih.gov. Accessed Jan 20, 2026.
20. Hall A, Evans K, Pribyl S. Cold injury in the United States military population: current trends and comparison with past conflicts. J Surg Educ. 2010;67(2):61-5.
21. Sheridan RL, Goverman JM, Walker TG. Diagnosis and treatment of frostbite. N Engl J Med. 2022;386(23):2213-20.
22. Knapik JJ, Reynolds KL, Castellani JW. Frostbite: pathophysiology, epidemiology, diagnosis, treatment, and prevention. J Spec Oper Med. 2020;20(4):123-35.
23. Binti Md Isa K, Kawasaki N, Ueyama K, Sumii T, Kudo S. Effects of cold exposure and shear stress on endothelial nitric oxide synthase activation. Biochem Biophys Res Commun. 2011;412(2): 318-22.
24. Nakamura H, Matsuzaki I, Hatta K, Nagase H, Nobokuni Y, Kambayashi Y, *et al*. Blood endothelin-1 and cold-induced vasodilation in patients with primary Raynauld's phenomenon and workers with vibration-induced white finger. Int Angiol. 2003;22(3):243-9.
25. McIntosh SE, Opacic M, Freer L, Grissom CK, Auerbach PS, Rodway GW, *et al*. Wilderness Medical Society. Wilderness Medical Society practice guidelines for the prevention and treatment of frostbite: 2014 update. Wilderness Environ Med. 2014;25(4 Suppl):S43-54.
26. Zook N, Hussmann J, Brown R, Russell R, Kucan J, Roth A, *et al*. Microcirculatory studies of frostbite injury. Ann Plast Surg. 1998; 40(3):246-53; discussion 254-5.
27. Brocato J, Chervona Y, Costa M. Molecular responses to hypoxia-inducible factor 1α and beyond. Mol Pharmacol. 2014;85(5):651-7.
28. Ziello JE, Jovin IS, Huang Y. Hypoxia-inducible factor (HIF)-1 regulatory pathway and its potential for therapeutic intervention in malignancy and ischemia. Yale J Biol Med. 2007;80(2):51-60.
29. Isozaki S, Tanaka H, Horioka K, Konishi H, Kashima S, Takauji S, *et al*. Hypoxia-induced nuclear translocation of β-catenin in the healing process of frostbite. Biochim Biophys Acta Mol Basis Dis. 2022;1868(6):166385.
30. Volkova MV, Boyarintsev VV, Trofimenko AV, Kovaleva EV, Othman AA, Melerzanov AV, *et al*. Local injection of bone-marrow derived mesenchymal stromal cells alters a molecular expression profile of a contact frostbite injury wound and improves healing in a rat model. Burns. 2023;49(2):432-43.
31. Tu H, Zhang D, Barksdale AN, Wadman MC, Muelleman RL, Li YL. Dexamethasone improves wound healing by decreased inflammation and increased vasculogenesis in mouse skin frostbite model. Wilderness Environ Med. 2020;31(4):407-17.
32. McIntosh SE, Freer L, Grissom CK, Rodway GW, Giesbrecht GG, McDevitt M, *et al*. Wilderness Medical Society clinical practice guidelines for the prevention and treatment of frostbite: 2024 update. Wilderness Environ Med. 2024;35(2):183-97.
33. Handford C, Buxton P, Russell K, Imray CE, McIntosh SE, Freer L, *et al*. Frostbite: a practical approach to hospital management. Extrem Physiol Med. 2014;3:7.
34. Cauchy E, Chetaille E, Marchand V, Marsigny B. Retrospective study of 70 cases of severe frostbite lesions: a proposed new classification scheme. Wilderness Environ Med. 2001;12(4):248-55.
35. Hallam MJ, Lo SJ, Imray C. Frostbite. In: Téot L, Meaume S, Akita S, Del Marmol V, Probst S, editors. Skin Necrosis. Cham: Springer; 2024. p. 1-13.
36. Millet JD, Brown RKJ, Levi B, Kraft CT, Jacobson JA, Gross MD, *et al*. Frostbite: spectrum of imaging findings and guidelines for management. Radiographics. 2016;36(7):2154-69.
37. Gao Y, Wang F, Zhou W, Pan S. Research progress in the

pathogenic mechanisms and imaging of severe frostbite. Eur J Radiol. 2021;137:109605.
38. Cauchy E, Chetaille E, Marchand V, Marsigny B. Retrospective study of 92 severe frostbite cases: a proposed new classification scheme. Am J Sports Med. 2001;29(4):500-3.
39. Cauchy E, Chetaille E, Lefevre M, Kerelou E, Marsigny B. The role of bone scanning in severe frostbite of the extremities: a retrospective study of 88 cases. Eur J Nucl Med. 2000;27(5):497-502.
40. Bruen KJ, Ballard JR, Morris SE, Cochran A, Edelman LS, Saffle JR. Reduction of the incidence of amputation in frostbite injury with thrombolytic therapy. Arch Surg. 2007;142(6):546-53.
41. Twomey JA, Peltier GL, Zera RT. Resolution of experimental frostbite injury with thrombolytic therapy. Acad Emerg Med. 2005;12(4):290-4.
42. Nygaard RM, Colonna E, Tilahun RA, Vang C, Punjabi G, Lacey A, *et al*. Time to thrombolytics and tissue salvage: assessing response following severe frostbite injury. J Burn Care Res. 2025;46(4):730-740.
43. Paine RE, Turner EN, Kloda D, Falank C, Chung B, Carter DW. Protocoled thrombolytic therapy for frostbite improves phalangeal salvage rates. Burns Trauma. 2020;8:tkaa008.
44. Barker JR, Haws MJ, Brown RE, Kucan JO, Moore WD. Magnetic resonance imaging of severe frostbite injuries. Ann Plast Surg. 1997;38(3):275-9.
45. Giesey RL, Parikh P, Samie FH. Use of indocyanine green fluorescence microangiography in the emergency department to assess frostbite injuries. Am J Emerg Med. 2022;60:228.e5-e7.
46. Raleigh SM, Samson M, Nygaard R, Endorf F, Walter J, Masters T. Bedside fluorescence microangiography for frostbite diagnosis in the emergency department. West J Emerg Med. 2022;23(6):872-877.
47. Lacey AM, Fey RM, Gayken JR, Endorf FW, Schmitz KR, Punjabi GV, *et al*. Microangiography: an alternative tool for assessing severe frostbite injury. J Burn Care Res. 2019;40(5):566-9.
48. Pessa JE, Howard MA, Crain CJ, Goretsky MJ, Adams WP Jr. Assessment of frostbite injury with laser Doppler imaging. Ann Plast Surg. 2012;69(1):80-2.
49. Yamada T, Inoue T, Ishikawa T. Thermographic assessment of frostbite injury in rabbits. Ann Plast Surg. 1993;30(2):148-53.
50. Buwalda G. Thermographic assessment of burns and frostbite. Bibl Radiol. 1969;5:178-81.
51. McIntosh SE, Freer L, Grissom CK, Auerbach PS, Rodway GW, Cochran A, *et al*. Wilderness medical society clinical practice guidelines for the prevention and treatment of frostbite: 2019 update. Wilderness Environ Med. 2019;30(4S):S19-32.
52. Hall A, Sexton J, Lynch B, Boecker F, Davis EP, Sturgill E, *et al*. Frostbite and immersion foot care. Mil Med. 2018;183(suppl 2):168-71.
53. Brownson E, Barnes JA, Dow J, Levy M, Quimby T, Roaten JB, *et al*. Frostbite care in Alaska 2024. Alaska Acute Frostbite Management Guidelines. 2024;2-7. https://health.alaska.gov/media/1enhyqld/alaska-acute-frostbite-management-guidelines.pdf
54. Emergency War Surgery. Chapter 27: Environmental Injuries. 5th ed. San Antonio (TX): Borden Institute; 2018. p. 396-9.
55. Poole A, Ahmed Y, Davidson M. The occasional frostbite. Can J Rural Med. 2024;29(1):30-6.
56. Mohr WJ, Jenabzadeh K, Ahrenholz DH. Cold injury. Hand Clin. 2009;25(4):481-96.
57. Orr K, Fainer D. Cold injuries in Korea during winter of 1950-51. Army Med Res Lab, Fort Knox, KY; 1951 Nov 1.
58. Hutchison RL, Miller HM, Michalke SK. The use of tPA in the treatment of frostbite: a systematic review. Hand (N Y). 2019;14(1):13-8.
59. Gonzaga T, Jenabzadeh K, Anderson CP, Mohr WJ, Endorf FW, Ahrenholz DH. Use of intra-arterial thrombolytic therapy for acute treatment of frostbite in 62 patients with review of thrombolytic therapy in frostbite. J Burn Care Res. 2016;37(4):e323-34.
60. Twomey JA, Peltier GL, Zera RT. An open-label study to evaluate the safety and efficacy of tissue plasminogen activator in treatment of severe frostbite. J Trauma. 2005;59(6):1350-4.
61. Wibbenmeyer L, Lacey AM, Endorf FW, *et al*. American Burn Association clinical practice guidelines on the treatment of severe frostbite. J Burn Care Res. 2024;45(3):541-56.
62. Harris E. FDA approves iloprost as first drug to treat severe frostbite. JAMA. 2024;331(11):907.
63. FDA. FDA approves first medication to treat severe frostbite. https://www.fda.gov/news-events/press-announcements/fda-approves-first-medication-treat-severe-frostbite. Accessed Sep 9, 2025.
64. Tsou PS, Palisoc PJ, Flavahan NA, Khanna D. Dissecting the cellular mechanism of prostacyclin analog iloprost in reversing vascular dysfunction in scleroderma. Arthritis Rheumatol. 2021;73(3):520-9.
65. Poole A, Gauthier J. Treatment of severe frostbite with iloprost in northern Canada. CMAJ. 2016;188(17-18):1255-8.
66. Cauchy E, Cheguillaume B, Chetaille E. A controlled trial of a prostacyclin and rt-PA in the treatment of severe frostbite. N Engl J Med. 2011;364(2):189-90.
67. Pandey P, Vadlamudi R, Pradhan R, *et al*. Severe frostbite in extreme altitude climbers – the Kathmandu iloprost experience. Wilderness Environ Med. 2018;29(3):366-74.
68. Poole A, Gauthier J, MacLennan M. Management of severe frostbite with iloprost, alteplase and heparin: a Yukon case series. CMAJ Open. 2021;9(2):E585-E591.
69. McIntosh SE, Freer L, Grissom CK, Auerbach PS, Rodway GW, Cochran A, *et al*. Wilderness Medical Society clinical practice guidelines for the prevention and treatment of frostbite: 2024 update. Wilderness Environ Med. 2024;35(2):183-97.
70. Zaramo TZ, Green JK, Janis JE. Practical review of the current management of frostbite injuries. Plast Reconstr Surg Glob Open. 2022;10(10):e4618.
71. Ekdahl M, Penninga L. Successful conservative treatment of severe frostbite lesions in a Greenlandic Inuit. BMJ Case Rep. 2017;2017:bcr2017219672.
72. Endorf FW, Nygaard RM. High cost and resource utilization of frostbite readmissions in the United States. J Burn Care Res. 2021;42(5):857-64.
73. Imray C, Grieve A, Dhillon S; Caudwell Xtreme Everest Research Group. Cold damage to the extremities: frostbite and non-freezing cold injuries. Postgrad Med J. 2009;85(1007):481-8.
74. Bangs CC. Hypothermia and frostbite. Emerg Med Clin North Am. 1984;2(3):475-87.
75. Juopperi K, Hassi J, Ervasti O, Drebs A, Näyhä S. Incidence of frostbite and ambient temperature in Finland, 1986-1995: a national study based on hospital admissions. Int J Circumpolar Health. 2002;61(4):352-62.
76. Carceller A, Javierre C, Ríos M, Viscor G. Amputation risk factors in severely frostbitten patients. Int J Environ Res Public Health. 2019;16(8):1351.

77. Sheridan RL, Goldstein MA, Stoddard FJ Jr, Walker TG. Case records of the Massachusetts General Hospital. Case 41-2009. A 16-year-old boy with hypothermia and frostbite. N Engl J Med. 2009;361(27):2654-62.
78. Joshi K, Goyary D, Mazumder B, Chattopadhyay P, Chakraborty R, Bhutia YD, *et al*. Frostbite: current status and advancements in therapeutics. J Therm Biol. 2020;93:102716.
79. Koljonen V, Andersson K, Mikkonen K, Vuola J. Frostbite injuries treated in the Helsinki area from 1995 to 2002. J Trauma. 2004;57(6):1315-20.
80. Groechenig E. Treatment of frostbite with iloprost. Lancet. 1994; 344(8930):1152-3.
81. Irarrázaval S, Besa P, Cauchy E, Pandey P, Vergara J. Case report of frostbite with delay in evacuation: field use of iloprost might have improved the outcome. High Alt Med Biol. 2018;19(4):382-87.
82. Lorentzen AK, Davis C, Penninga L. Interventions for frostbite injuries. Cochrane Database Syst Rev. 2020;12(12):CD012980.
83. Hayes DW Jr, Mandracchia VJ, Considine C, Webb GE. Pentoxifylline. Adjunctive therapy in the treatment of pedal frostbite. Clin Podiatr Med Surg. 2000;17(4):715-22.
84. Norheim AJ, Mercer J, Musial F, de Weerd L. A new treatment for frostbite sequelae; botulinum toxin. Int J Circumpolar Health. 2017;76(1):1273677.
85. Robins M, Hendriksen S, Cooper JS. Hyperbaric Management of Frostbite. [Updated 2025 May 2]. In: StatPearls [Internet]. Treasure Island (FL): StatPearls Publishing; 2025 Jan. Available from: https://www.ncbi.nlm.nih.gov/books/NBK448115/.
86. Wu Y, Duff E. Management of frostbite injury in primary care. J Nurse Pract. 2024;20(2):104897.
87. Gupta A, Soni R, Ganguli M. Frostbite – manifestation and mitigation. Burns Open. 2021;5(3):96-103.
88. Pedro MA, Janiszewski M, Janiszewski TA, Silva E, Knobel E, Laurindo FRM. Apoptosis of vascular cells in culture and reactive oxygen species generation following exposure to plasma of septic patients. Crit Care. 2001;5(Suppl 3): P22.
89. Sekiguchi A, Ishikawa M, Uchiyama A, Yokoyama Y, Ogino S, Torii R, *et al*. Rapid thawing enhances tissue destruction in a mouse model of cutaneous cryoablation: insights into oxidative stress and neutrophil activation. J Dermatol Sci. 2025;118(1):9-17.
90. Hu J, Li H, Geng X, Jiao L, Song H, Lou L, *et al*. Pathophysiologic determination of frostbite under high altitude environment simulation in Sprague-Dawley rats. Wilderness Environ Med. 2016;27(3):355-63.
91. Auerbach LJ, Galvez MG, De Clerck BK, Glotzbach J, Wehner MR, Chang EI, *et al*. A novel mouse model for frostbite injury. Wilderness Environ Med. 2013;24(2):94-104.
92. Ummadisetty O, Akhilesh, Gadepalli A, Chouhan D, Tiwari V. Development and validation of clinically mimicable model of frostbite injury-induced chronic pain. Cell Signal. 2024;115: 111028.
93. Junila J, Kaarela O, Mäkäräinen H, Waris T. Assessment of tissue viability by thermography after experimentally produced frostbite of the rabbit ear. Acta Radiol. 1993;34(6):622-4.
94. Schoning P, Hamlet MP. Experimental frost-bite in Hanford miniature swine. I. Epithelial changes. Br J Exp Pathol. 1989;70(1): 41-9.
95. Rothenberger J, Held M, Jaminet P, Schiefer J, Petersen W, Schaller HE, *et al*. Development of an animal frostbite injury model using the Goettingen-Minipig. Burns. 2014;40(2):268-73.
96. Abbas Q, Jeong W, Lee SW. Explainable AI in clinical decision support systems: a meta-analysis of methods, applications, and usability challenges. Healthcare (Basel). 2025;13(17):2154.
97. Rahman MM, Masry ME, Gnyawali SC, Xue Y, Gordillo G, Wachs JP. AI-driven integrated system for burn depth prediction with electronic medical records: algorithm development and validation. JMIR Med Inform. 2025;13:e68366.
98. Cindass RJ Jr, Cancio TS, Cancio JM, Pruskowski KA, Park SE, Shingleton SK, *et al*. Management of multiple frostbite casualties at a burn center: San Antonio, Texas, 12-20 February 2021. Burns. 2023;49(8):1990-6.
99. Persitz J, Essa A, Ner EB, Assaraf E, Avisar E. Frostbite of the extremities - recognition, evaluation and treatment. Injury. 2022; 53(10):3088-93.

https://doi.org/10.1016/j.mmr.2026.100007
Cite this article as: Obaidi N, Agee O, Yau I, Moritz R, Nuutila K. Frostbite: diagnosis, treatment, prognosis, and future directions. *Mil Med Res*. 2026;13(1):100007.