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WILDERNESS MEDICAL SOCIETY CLINICAL PRACTICE GUIDELINES

Wilderness Medical Society Clinical Practice Guidelines for the Prevention and Treatment of Frostbite: 2019 Update

Scott E. McIntosh, MD, MPH [1]; Luanne Freer, MD [2,3]; Colin K. Grissom, MD [4]; Paul S. Auerbach, MD, MS [5]; George W. Rodway, PhD, APRN [6]; Amalia Cochran, MD [7]; Gordon G. Giesbrecht, MD [8]; Marion McDevitt, DO, MPH [9]; Christopher H. Imray, MD [10]; Eric L. Johnson, MD [11]; Prativa Pandey, MD [12]; Jennifer Dow, MD [13]; Peter H. Hackett, MD [14,15]

[1]Division of Emergency Medicine, University of Utah, Salt Lake City, UT; [2]Everest Base Camp Medical Clinic, Nepal; [3]Yellowstone National Park, WY; [4]Division of Critical Care Medicine, Intermountain Medical Center, Salt Lake City, UT; [5]Department of Emergency Medicine, Stanford University, School of Medicine, Palo Alto, CA; [6]College of Nursing and School of Medicine, UC Davis, Davis, CA; [7]Department of Surgery, The Ohio State University, Columbus, OH; [8]Faculty of Kinesiology and Recreation Management, Departments of Anesthesia and Emergency Medicine, University of Manitoba, Winnipeg, Canada; [9]Emergency Medicine, Peace Health Ketchikan Medical Center, Ketchikan, AK; [10]Warwick Medical School, University Hospital Coventry and Warwickshire NHS Trust, Coventry, UK; [11]Wound & Hyperbaric Medicine, Bozeman Health, Bozeman, MT; [12]CIWEC Hospital, Kathmandu, Nepal; [13]Denali National Park and Preserve, AK; [14]Division of Emergency Medicine, Altitude Research Center, University of Colorado Denver School of Medicine, Denver, CO; [15]Institute for Altitude Medicine, Telluride, CO

The Wilderness Medical Society convened an expert panel to develop a set of evidence-based guidelines for prevention and treatment of frostbite. We present a review of pertinent pathophysiology. We then discuss primary and secondary prevention measures and therapeutic management. Recommendations are made regarding each treatment and its role in management. These recommendations are graded on the basis of the quality of supporting evidence and balance between the benefits and risks or burdens for each modality according to methodology stipulated by the American College of Chest Physicians. This is an updated version of the guidelines published in 2014.

Keywords: hypothermia, rewarming, aloe vera, thrombolysis, tPA, iloprost

Introduction

The Wilderness Medical Society (WMS) convened an expert panel to develop a set of evidence-based guidelines for prevention and treatment of frostbite to guide clinicians and first responders and disseminate knowledge about best practices in this area of clinical care. We present the main prophylactic and therapeutic modalities and make recommendations about their role in injury management. Recommendations are graded on the basis of the quality of supporting evidence and balance between the benefits and risks or burdens for each modality. We then provide suggested approaches for prevention and management that incorporate these recommendations.

The original expert panel was convened at the 2010 Annual Winter Meeting of the WMS in Park City, UT. Members were selected on the basis of their clinical or research experience. Relevant articles were identified through the MEDLINE database using the search terms frostbite, frostbite management, prehospital frostbite treatment, prehospital frostbite management, frostbite prevention, first aid frostbite treatment, and first aid frostbite and were restricted to the English language. Studies in these categories were reviewed, and level of evidence was assessed. The panel used a consensus approach to develop recommendations regarding each modality and graded each recommendation according to criteria stipulated by the American College of Chest Physicians statement on grading recommendations and strength of evidence in clinical guidelines (online Supplementary Table 1).[1] This is an updated version of the guidelines published in 2014.[2]

Corresponding author: Scott E. McIntosh, MD, MPH, University of Utah, Division of Emergency Medicine, 50 North Medical Drive, Salt Lake City, UT 84132; e-mail: scott.mcintosh@hsc.utah.edu.

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Pathophysiology of frostbite

Frostbite is a freezing injury that may be divided into 4 overlapping pathologic phases: prefreeze, freeze–thaw, vascular stasis, and late ischemic. The prefreeze phase consists

of tissue cooling with accompanying vasoconstriction and ischemia and without actual ice crystal formation. Neuronal cooling and ischemia produce hyperesthesia or paresthesia. In the freeze−thaw phase, ice crystals form intracellularly (during a more rapid-onset freezing injury) or extracellularly (during a slower freeze), causing protein and lipid derangement, cellular electrolyte shifts, cellular dehydration, cell membrane lysis, and cell death.[3] The thawing process may initiate ischemia, reperfusion injury, and an inflammatory response. In the vascular stasis phase, vessels fluctuate between constriction and dilation; blood may leak from vessels or coagulate within them.[4−6] The late ischemic phase results from progressive tissue ischemia and infarction from a cascade of events, including inflammation mediated by thromboxane A_2, prostaglandin F_2alpha, bradykinin, and histamine; intermittent vasoconstriction of arterioles and venules; continued reperfusion injury; showers of emboli coursing through the microvessels[7,8]; and thrombus formation in larger vessels.[9] Destruction of the microcirculation is the main factor leading to cell death.[10] The initial cellular damage caused by ice crystals and the subsequent postthawing processes are made worse if refreezing follows thawing of injured tissues.[11,12]

Classification of frostbite

Frostnip is superficial nonfreezing cold injury associated with intense vasoconstriction on exposed skin, usually cheeks, ears, or nose. Ice crystals, appearing as frost, form on the skin surface. Frostnip is distinct from and may precede frostbite. With frostnip, ice crystals do not form within the tissue and tissue loss does not occur. Numbness and pallor resolve quickly after warming the skin with appropriate clothing, direct contact, breathing with cupped hands over the nose, or gaining shelter. No long-term damage occurs. Frostnip signals conditions favorable for frostbite; appropriate action should be undertaken immediately to prevent injury.

Frostbite has historically been divided into 4 tiers or "degrees" of injury following the classification scheme for thermal burn injury. These classifications are based on acute physical findings and advanced imaging after rewarming.[13] The classifications can be difficult to assess in the field before rewarming because the still-frozen tissue is hard, pale, and anesthetic. An alternate 2-tiered classification more appropriate for field use (after rewarming but before imaging) is suggested with the following the 4-tier classification:

- First-degree frostbite causes numbness and erythema. A white or yellow, firm, and slightly raised plaque develops in the area of injury. No gross tissue infarction occurs; there may be slight epidermal sloughing. Mild edema is common.
- Second-degree frostbite injury causes superficial skin vesiculation; a clear or milky fluid is present in the blisters, surrounded by erythema and edema.
- Third-degree frostbite causes deeper hemorrhagic blisters, indicating that the injury has extended into the reticular dermis and beneath the dermal vascular plexus.
- Fourth-degree frostbite extends completely through the dermis and involves the comparatively avascular subcutaneous tissues, with necrosis extending into muscle and bone.

For field classification, after spontaneous or formal rewarming but before imaging, we favor the following 2-tier classification scheme:

- *Superficial*—no or minimal anticipated tissue loss, corresponding to first- and second-degree injury.
- *Deep*—anticipated tissue loss, corresponding to third- and fourth-degree injury.

Severity of frostbite may vary within a single extremity.

Once thawing occurs and a patient reaches a field clinic or hospital, one can further classify or characterize the frostbite injury via 2 additional methods. The Hennepin score[14] uses a system similar to that for measuring burns by total body surface area. The effect of treatment can then be quantified retrospectively. The Cauchy classification method[13] measures extent of frostbite anatomically using the following grades: 0—no lesion; 1—lesion on the distal phalanx; 2—lesion on the middle phalanx or proximal phalanx for the thumb/big toe; 3—lesion on the proximal phalanx except for the thumb/big toe; 4—lesion on the metacarpal/metatarsal; 5—lesion on the carpal/tarsal. Although not validated, grades correlate well with bone scans and clinical outcomes and may assist caregivers in predicting tissue loss. The Cauchy classification method may assist caregivers in predicting amputation risk, which helps to inform evacuation decisions. For example, a necrotic fingertip (labeled grade 4 by the 4-tiered system but unlikely to involve significant amputation) would be designated a grade 1 on the Cauchy classification method, designating lower severity. Higher grades in the Cauchy classification method designate more proximal injuries with greater risk for functionally important amputation.

Prevention

The adage that "prevention is better than treatment" is especially true for frostbite, which is typically preventable and

often not improved by treatment. Underlying medical problems may increase risk of frostbite, so prevention must address both environmental and health-related aspects. Frostbite injury occurs when tissue heat loss exceeds the ability of local tissue perfusion to prevent freezing of soft tissues (blood flow delivers heat). One must both ensure adequate perfusion and minimize heat loss to prevent frostbite. The adventurer should recognize cold-induced "numbness" as a warning that frostbite injury may be imminent if protective or avoidance measures are not taken to decrease tissue cooling. Subsequent loss of sensation does not mean the situation has improved; rather, receptors and nerves are not conducting pain/cold signals because they are nearing the freezing point.

MAINTAINING PERIPHERAL PERFUSION

Preventive measures to ensure local tissue perfusion include: 1) maintaining adequate core temperature and body hydration; 2) minimizing the effects of known diseases, medications, and substances (including awareness and symptoms of alcohol and drug use) that might decrease perfusion; 3) covering all skin and the scalp to insulate from the cold; 4) minimizing blood flow restriction, such as occurs with constrictive clothing, footwear, or immobility; 5) ensuring adequate nutrition; and 6) using supplemental oxygen in severely hypoxic conditions (eg, >7500 m). ***Recommendation Grade:*** 1C.

EXERCISE

Exercise is a specific method to maintain peripheral perfusion. Exercise enhances the level and frequency of cold-induced peripheral vasodilation. In one study, exercise resulted in cold-induced peripheral vasodilation in the toes of 58% of exercising subjects vs 28% in nonexercising subjects.[15] Another study found increased skin temperature in the hands during exercise.[16] However, using exercise to increase warmth can lead to exhaustion, with subsequent profound systemic heat loss should exhaustion occur. Recognizing this caveat, exercise and its associated elevation in core and peripheral temperatures can be protective in preventing frostbite. ***Recommendation Grade:*** 1B.

PROTECTION FROM COLD

Measures should be taken to minimize exposure of tissue to cold. These measures include the following: 1) avoiding environmental conditions that predispose to frostbite, specifically below -15°C, even with low wind speeds[17]; 2) protecting skin from moisture, wind, and cold; 3) avoiding perspiration or wet extremities; 4) increasing insulation and skin protection (eg, by adding clothing layers, changing from gloves to mitts); 5) ensuring beneficial behavioral responses to changing environmental conditions (eg, not being under the influence of illicit drugs, alcohol, or extreme hypoxemia)[18]; 6) using chemical hand and foot warmers and electric foot warmers to maintain peripheral warmth (note: warmers should be close to body temperature before being activated and must not be placed directly against skin or constrict flow if used within a boot); 7) regularly checking oneself and the group for extremity numbness or pain and warming the digits and/or extremities as soon as possible if there is concern that frostbite may be developing; 8) recognizing frostnip or superficial frostbite before it becomes more serious; and 9) minimizing duration of cold exposure. Emollients do not protect against—and might even increase—risk of frostbite.[19] The time that a digit or extremity can remain numb before developing frostbite is unknown; thus, digits or extremities with paresthesia should be warmed as soon as possible. An extremity at risk for frostbite (eg, numbness, poor dexterity, pale color) should be warmed with adjacent body heat from the patient or a companion, using the axilla or abdomen. ***Recommendation Grade:*** 1C.

Field treatment and secondary prevention

If a body part is frozen in the field, the frozen tissue should be protected from further damage. Remove jewelry or other constrictive extraneous material from the body part. Do not rub or apply ice or snow to the affected area.[20]

REFREEZING INJURY

A decision must be made whether to thaw the tissue. If environmental conditions are such that thawed tissue could refreeze, it is safer to keep the affected part frozen until a thawed state can be maintained. Prostaglandin and thromboxane release associated with the freeze—thaw cycle[20–22] causes vasoconstriction, platelet aggregation, thrombosis, and, ultimately, cellular injury. Refreezing thawed tissue further increases release of these mediators, and significant morbidity may result. One must absolutely avoid refreezing if field thawing occurs. ***Recommendation Grade:*** 1B.

SPONTANEOUS OR PASSIVE THAWING

Most frostbite thaws spontaneously and should be allowed to do so if rapid rewarming (described in the following) cannot be readily achieved. Do not purposefully keep tissue below freezing temperatures because this will increase the duration that the tissue is frozen and might result in more proximal freezing and greater morbidity. If environmental and situational conditions allow for spontaneous or slow thawing, tissue should be allowed to thaw. ***Recommendation Grade:*** 1C.

Strategies for 2 scenarios are presented:

Scenario 1: The frozen part has the potential for refreezing and is not actively thawed.

Scenario 2: The frozen part is thawed and kept warm without refreezing until evacuation is completed.

THERAPEUTIC OPTIONS FOR BOTH SCENARIOS

Many of these guidelines parallel the State of Alaska cold injuries guidelines.[23] Therapeutic options include the following:

Treatment of hypothermia

No studies examine concurrent hypothermia and frostbite. Hypothermia frequently accompanies frostbite and causes peripheral vasoconstriction that impairs blood flow to the extremities. Mild hypothermia may be treated concurrently with frostbite injury. Moderate and severe hypothermia should be treated effectively before treating frostbite injury. ***Recommendation Grade:*** 1C.

Hydration

Vascular stasis can result from frostbite injury. No studies have specifically examined the effect of hydration status on frostbite outcomes, but it is believed that appropriate hydration and avoidance of hypovolemia are important for frostbite recovery. Oral fluids may be given if the patient is alert, capable of purposeful swallowing, and not vomiting. If the patient is nauseated or vomiting or has an altered mental status, IV normal saline should be given to maintain normal urine output. Intravenous fluids should optimally be warmed (minimally to 37°C but preferably to 40 to 42°C with a method that has been proven to be effective in the present environmental conditions) before infusion and be infused in small (eg, 250 mL), rapid boluses because slow infusion will result in fluid cooling and even freezing as it passes through the tubing. Fluid administration should be optimized to prevent clinical dehydration. ***Recommendation Grade:*** 1C.

Low molecular weight dextran

Intravenous low molecular weight dextran (LMWD) decreases blood viscosity by preventing red blood cell aggregation and formation of microthrombi and can be given in the field once it has been warmed. In some animal studies, the extent of tissue necrosis was found to be significantly less than in control subjects when LMWD was used[24–27] and was more beneficial if given early.[28] In one animal trial,[28] tissue in the LMWD group thawed slightly more rapidly, but overall tissue loss was no different from that of control animals. Give a test dose before administration because of the low risk of anaphylaxis. This low risk of anaphylaxis should not deter administration. The slight risk of bleeding is minimal, and benefits seem to outweigh this risk; however, availability is limited in the United States. The use of LMWD has not been evaluated in combination with other treatments such as thrombolytics. LMWD should be given if the patient is not being considered for other systemic treatments, such as thrombolytic therapy. ***Recommendation Grade:*** 2C.

Ibuprofen

Nonsteroidal anti-inflammatory drugs (NSAIDs) block the arachidonic acid pathway and decrease production of prostaglandins and thromboxanes.[29] These mediators can lead to vasoconstriction, dermal ischemia, and further tissue damage. No studies have demonstrated that any particular anti-inflammatory agent or dosing is clearly related to outcome. Aspirin has been proposed as an option and is used in many parts of the world for anti-inflammatory and platelet inhibition effects. One rabbit ear model study showed 23% tissue survival with aspirin vs 0% in the control group.[30] However, aspirin theoretically blocks production of certain prostaglandins that are beneficial to wound healing,[31] and the authors of the rabbit ear model study recommend ibuprofen in their treatment algorithm. No studies specifically compare aspirin with ibuprofen in frostbite. Ibuprofen should be started in the field at a dose of 12 $mg \cdot kg^{-1}$ per day divided twice daily (minimum to inhibit harmful prostaglandins[29]) to a maximum of 2400 $mg \cdot d^{-1}$ divided 4 times daily. ***Recommendation Grade:*** 2C.

SPECIFIC RECOMMENDATIONS—SCENARIO 1

Therapeutic options for frostbite in Scenario 1 (no active thawing) include the following:

Dressings

No evidence supports applying a dressing to a frostbitten part intended to remain frozen until rewarming can safely be achieved. If this is considered, it should only be done if practical and will not interfere with mobility. Bulky, clean, and dry gauze or sterile cotton dressings should be applied to the frozen part and between the toes and fingers. ***Recommendation Grade:*** 2C.

Ambulation and protection

If at all possible, a frozen extremity should not be used for walking, climbing, or other maneuvers until definitive care is reached. If use of the frozen extremity for mobility is considered, a risk-benefit analysis must consider the potential

for further trauma and possible poorer outcome. Although it is reasonable to walk on a foot with frostbitten toes for evacuation purposes, it is inadvisable to walk on an entirely frostbitten foot because of the potential for resulting morbidity. This risk is theoretical and based on the panel's opinion. Mills described frostbite patients who ambulated on frozen extremities for days and sustained no or limited amputation.[32] If using a frozen extremity for locomotion or evacuation is unavoidable, the extremity should be padded, splinted, and kept as immobile as possible to minimize additional trauma. ***Recommendation Grade:*** 2C.

SPECIFIC RECOMMENDATIONS—SCENARIO 2

Therapeutic options for frostbite in Scenario 2 (thawing and continued warming) include the following:

Rapid field rewarming of frostbite

Field rewarming by warm water bath immersion can and should be performed if the proper resources are available and definitive care is more than 2 h distant. Other heat sources (eg, fire, space heater, oven, heated rocks) should be avoided because of the risk of thermal burn injury. Rapid rewarming by water bath has been found to result in better outcomes than slow rewarming.[20,27,32] Field rewarming should only be undertaken if the frozen part can be kept thawed and warm until the victim arrives at definitive care. Water should be heated to 37 to 39°C (98.6 to 102.2°F), using a thermometer to maintain this range.[33] If a thermometer is not available, a safe water temperature can be determined by placing a caregiver's uninjured hand in the water for at least 30 s to confirm that the water temperature is tolerable and will not cause burn injury. Circulation of water around the frozen tissue will help maintain correct temperature.[34,35] Because the water may cool quickly after the rewarming process is started, the water should be continuously and carefully warmed to the target temperature. If the frozen part is being rewarmed in a pot, skin should not press against the bottom or sides. Rewarming is complete when the involved part takes on a red or purple appearance and becomes soft and pliable to the touch. This is usually accomplished in approximately 30 min, but the time is variable depending on the extent and depth of injury. The affected tissues should be allowed to air dry or be gently dried with a blotting technique (not rubbing) to minimize further damage. Under appropriate circumstances, this method of field rewarming is the first definitive step in frostbite treatment. ***Recommendation Grade:*** 1B.

Antiseptic solution

Most injuries do not become infected, but adding an antiseptic solution (eg, povidone-iodine, chlorhexidine) to the rewarming water has theoretical benefits of reducing skin bacteria. Evidence for this practice does not exist for frostbite care, however. Adding an antiseptic solution to the water while rewarming is unlikely to be harmful and might reduce the risk for cellulitis if severe edema is present in the affected extremity. ***Recommendation Grade:*** 2C.

Pain control

During rewarming, pain medication (eg, NSAIDs or an opiate analgesic) should be given to control symptoms as dictated by individual patient situation. ***Recommendation Grade:*** 1C.

Spontaneous or passive thawing

According to the foregoing guidelines, rapid rewarming is strongly recommended. If field rewarming is not possible, spontaneous or slow thawing should be allowed. Slow rewarming is accomplished by moving to a warmer location (eg, tent or hut) and warming with adjacent body heat from the patient or a caregiver, as previously described. The expert panel agrees that slow thawing is a reasonable course of action to initiate the rewarming process if it is the only means available. ***Recommendation Grade:*** 1C.

Debridement of blisters

Debridement of blisters should not be routinely performed in the field. If a clear, fluid-filled blister is tense and at high risk for rupture during evacuation, blister aspiration and application of a dry gauze dressing should be performed in the field to minimize infection risk. Hemorrhagic bullae should not be aspirated or debrided in the field. These recommendations are common practice but lack evidence beyond case series.[29] ***Recommendation Grade:*** 2C.

Topical aloe vera

Aloe vera ointment has been shown in an observational study[36] and an animal model[30] to improve frostbite outcome by reducing prostaglandin and thromboxane formation. Topical agents do not penetrate far into tissues, however, so aloe vera is theoretically only beneficial for superficially injured areas. The study supporting the benefit of aloe vera examined its application on unroofed blebs where it would be able to penetrate underlying tissue. Topical aloe vera should be applied to thawed tissue before application of dressings. ***Recommendation Grade:*** 2C.

Dressings

Bulky, dry gauze dressings should be applied to the thawed parts for protection and wound care. Substantial edema should be anticipated, so circumferential dressings should be wrapped loosely to allow for swelling without placing pressure on the underlying tissue. ***Recommendation Grade:*** 1C.

Ambulation and protection

A risk-benefit analysis must consider the potential for further trauma and, ultimately, potentially higher morbidity if a thawed part is used for ambulation. For example, it might be reasonable to walk on a foot with thawed toes for evacuation purposes, but it is inadvisable to walk on a recently thawed frostbitten foot because of the potential resulting morbidity. Very little evidence is available to guide recommendations. In one study, mobilization within 72 h after thawing did not affect tissue loss, complications, or hospital length of stay.[37] After the rewarming process, swelling should be anticipated. If passive thawing has occurred, boots (or inner boots) may need to be worn continuously to compress swelling. Boots that were removed for active rewarming may not be able to be re-donned if tissue swelling has occurred during the warming process. The panel's clinical experience supports the concept that a recently thawed extremity should ideally not be used for walking, climbing, or other maneuvers and should be protected to prevent further trauma.[36,38] ***Recommendation Grade:*** 2C.

Elevation of extremity

If possible, the thawed extremity should be elevated above the level of the heart, which might decrease formation of dependent edema. ***Recommendation Grade:*** 1C.

Oxygen

Recovery of thawed tissue partly depends on the level of tissue oxygenation in the postfreezing period. One small study that measured hand temperature at normobaric hypoxia found decreased skin temperatures with decreasing F_IO_2.[39] However, hyperoxia has been found to cause vasoconstriction in the extremities[40]; therefore, oxygen should not be applied routinely to patients who are not hypoxic. Although evidence is lacking to support use of supplemental oxygen for frostbite, oxygen may be delivered by face mask or nasal cannula if the patient is hypoxic (oxygen saturation <88%) or at high altitude above 4000 m. ***Recommendation Grade:*** 2C.

For a summary of the suggested approach to the field treatment of frostbite, see Table 1.

Immediate medical therapy—hospital (or high-level field clinic)

Once the patient reaches the hospital or field clinic, a number of treatments should be initiated. After reaching the hospital or field clinic, potential therapeutic options for frostbite include the following:

TREATMENT OF HYPOTHERMIA

Similar recommendations apply to hospital or field clinic treatment of hypothermia before frostbite treatment (see previous). ***Recommendation Grade:*** 1C.

HYDRATION

Similar recommendations apply in the hospital or field clinic regarding hydration (see previous). ***Recommendation Grade:*** 1C.

LOW MOLECULAR WEIGHT DEXTRAN

Similar recommendations apply in the hospital or field clinic regarding LMWD (see previous). ***Recommendation Grade:*** 2C.

RAPID REWARMING OF FROZEN TISSUES

Frozen tissue should be assessed to determine whether spontaneous thawing has occurred. If tissue is completely thawed, further rewarming will not be beneficial. Rapid rewarming should be undertaken according to the field protocol described previously if the tissue remains partially or completely frozen. ***Recommendation Grade:*** 1B.

MANAGEMENT OF BLISTERS

Clear or cloudy blisters contain prostaglandins and thromboxanes that may damage underlying tissue. Hemorrhagic blisters are thought to signify deeper tissue damage extending into the dermal vascular plexus. Common practice is to

Table 1. Summary of field treatment of frostbite (>2 h from definitive care)

Treat hypothermia or serious trauma
1. Remove jewelry or other extraneous material from the body part.
2. Rapidly rewarm in water heated and maintained between 37 and 39°C (98.6 and 102.2°F) until area becomes soft and pliable to the touch (approximately 30 min); allow spontaneous or passive thawing if rapid rewarming is not possible.
3. Ibuprofen (12 $mg \cdot kg^{-1}$ per day divided twice daily) if available.
4. Pain medication (eg, opiate) as needed.
5. Air dry (ie, do not rub at any point).
6. Protect from refreezing and direct trauma.
7. Apply topical aloe vera cream or gel if available.
8. Dry, bulky dressings.
9. Elevate the affected body part if possible.
10. Systemic hydration.
11. Avoid ambulation on thawed lower extremity (unless only distal toes are affected).

drain clear blisters (eg, by needle aspiration) while leaving hemorrhagic blisters intact.[34,36,38,41,42] Although this approach to frostbite blister management is recommended by many authorities, comparative studies have not been performed and data are insufficient to make absolute recommendations. Some authors argue that unroofing blisters might lead to the desiccation of exposed tissue and that blisters should only be removed if they are tense, likely to break or be infected, or interfere with the patient's range of motion.[43] In a remote field situation, draining or unroofing blisters may not be under control of the provider. Blisters most often will have been broken by the patient's boots. In this case, the most important treatment is applying aloe vera and a sterile dressing to the unroofed blister. Debridement or aspiration of clear, cloudy, or tense blisters is at the provider's discretion, with consideration of patient circumstances, until better evidence becomes available. ***Recommendation Grade:*** 2C.

TOPICAL ALOE VERA

Topical aloe vera cream or gel should be applied to the thawed tissue before application of dressings. Aloe vera is reapplied at each dressing change or every 6 h.[36] ***Recommendation Grade:*** 2C.

SYSTEMIC ANTIBIOTICS

Frostbite is not an inherently infection-prone injury. Therefore, antibiotic administration specifically for preventing infection during or after frostbite injury is not supported by evidence. Some authorities reserve antibiotics for situations when edema occurs after thawing because of the notion that edema increases skin susceptibility to infection by gram-positive bacteria.[38] However, this practice is not based on evidence. Systemic antibiotics, either oral or parenteral, should be administered to patients with significant trauma, other potential infectious sources, or signs and symptoms of cellulitis or sepsis. ***Recommendation Grade:*** 1C.

TETANUS PROPHYLAXIS

Tetanus prophylaxis should be administered according to standard guidelines. ***Recommendation Grade:*** 1C.

IBUPROFEN

If NSAIDs have not been initiated in the field, ibuprofen should be administered at a dose of 12 $mg \cdot kg^{-1}$ divided twice daily (to inhibit harmful prostaglandins but remain less injurious to the gastrointestinal system[29]) until the frostbite wound is healed or surgical management occurs (typically for 4 to 6 wk). ***Recommendation Grade:*** 2C.

THROMBOLYTIC THERAPY

The goal of thrombolytic therapy in frostbite injury is to lyse and clear microvascular thromboses. For deep frostbite injury with potential significant morbidity, angiography and use of either IV or intra-arterial tissue plasminogen activator (tPA) within 24 h of thawing may salvage some or all tissue at risk. A retrospective, single-center review by Bruen et al[44] demonstrated reduction in digital amputation rates from 41% in those patients who did not receive tPA to 10% in patients receiving tPA within 24 h of injury. The 20-y series presented by the Regions Hospital group found that two-thirds of patients who received intra-arterial tPA responded well and that amputation rate correlated closely with angiographic findings.[45] The Massachusetts General Hospital group has proposed a screening and treatment tool for thrombolytic management of frostbite based on a case report and their evaluation of the Utah and Minneapolis experiences.[46] Twomey et al[47] from Hennepin County Medical Center have developed a specific protocol based on a small group of good outcomes with intravenous tPA. Further study is needed to compare intra-arterial vs IV tPA on tissue salvage and functional outcome. Animal studies demonstrate benefit from thrombolytics.[48]

When considering using a thrombolytic, a risk-benefit analysis should be performed. Only deep injuries with potential for significant morbidity (eg, extending into the proximal interphalangeal joints of digits) should be considered for thrombolytic therapy. Potential risks of tPA include systemic and catheter site bleeding, compartment syndrome, and failure to salvage tissue. The long-term, functional consequences of digit salvage using tPA have not been fully evaluated.

Thrombolytic treatment should be undertaken in a facility familiar with the technique and with intensive care monitoring capabilities. If a frostbite patient is being cared for in a remote area, transfer to a facility with tPA administration and monitoring capabilities should be considered if tPA can be started within 24 h of tissue thawing. Time to thrombolysis appears to be very important, with best outcomes within 12 h and ideally as soon as possible. Recent work from Hennepin County has found that each hour of delay of thrombolytic therapy results in a 28% decrease in salvage.[49] Rare use of tPA in the field has shown variable success[50] and should only be undertaken with extreme caution because bleeding complications may be impossible to detect and treat. If other treatment options are limited or unavailable, tPA should be considered for field treatment only of severe frostbite extending to the proximal interphalangeal joint or more proximally (eg, Cauchy classification grade 3 to 5).

Method of administration

Dosing is typically a 3 mg bolus (30 mL of 0.1 $mg \cdot mL^{-1}$ solution) followed by infusion of 1 $mg \cdot mL^{-1}$ (10 $mL \cdot h^{-1}$) until specialists (eg, vascular, burn, radiology) recommend discontinuation. Heparin is administered concurrently: 500 units $\cdot h^{-1}$.[51]

Intra-arterial angiography or IV pyrophosphate scanning should be used to evaluate the initial injury and monitor progress after tPA administration as directed by local protocol and resources. As of the end of 2018,[52] the following have been published on tPA use in frostbite: 1 randomized controlled prospective trial (tPA plus iloprost, 16 patients),[53] 3 retrospective cohort studies (59 patients),[44,49,54] 8 retrospective case series (130 patients),[47,55–61] and 3 case reports.[46,62,63] Although further studies are needed to determine the absolute efficacy of tPA for frostbite injury and to compare intra-arterial tPA to IV prostacyclin, we recommend IV or intra-arterial tPA within 24 h of injury as a reasonable choice in an environment with appropriate monitoring capabilities. ***Recommendation Grade:*** 1C.

IMAGING

In patients with delayed presentation (4-24 h from the time of the frostbite thawing), noninvasive imaging with technetium pyrophosphate[13] or magnetic resonance angiography[64] can be used at an early stage to predict the likely levels of tissue viability for amputation. Cauchy et al[13] described the combination of a clinical scoring system and technetium scanning to successfully predict subsequent level of amputation on day 2 after frostbite rewarming. Single photon emission computed tomography (CT)/CT combines the anatomic precision of CT with the functional vascular information obtained from multiphase bone scintigraphy. Kraft et al used single photon emission CT/CT for 7 patients with frostbite and found it improved surgical planning for deep frostbite injuries by enabling early and precise anatomic localization of nonviable tissues.[65,66]

If available, appropriate imaging should be used to assess tissue viability and guide timing and extent of amputation. ***Recommendation Grade:*** 1C.

Other potential useful imaging techniques include Doppler ultrasound[55]; triple phase technitium[58,67]; indocyanine green microangiography[68]; and thermal imaging.[39] Although some of these techniques show potential, further studies are required to determine their exact role.

ILOPROST

Iloprost, a prostacyclin (PGI2) analogue, is a potent vasodilator that also inhibits platelet aggregation, down-regulates lymphocyte adhesion to endothelial cells,[69] and may have fibrinolytic activity.[70] Intravenous iloprost was first used for treatment of frostbite by Groechenig in 1994, in 5 patients with second- and third-degree frostbite. He infused iloprost daily, starting at 0.5 $ng \cdot kg^{-1}$ and increasing to 2.0 $ng \cdot kg^{-1}$ total dose over 3 d, and then continued for between 14 and 42 d.[71] Recovery without amputation was achieved in all patients.

A randomized trial by Cauchy et al assessed the efficacy of aspirin plus: 1) buflomedil, an alpha-blocker vasodilator; 2) iloprost; or 3) intravenous tPA plus iloprost.[53] Forty-seven patients with severe frostbite, with 407 digits at risk, were randomly assigned to 8 d of treatment with the 3 different regimens. Iloprost alone (0% amputation rate) was found superior to tPA plus iloprost (19%) and buflomedil (60%) groups. A limitation of this study was that ischemia was not documented with angiography or technetium scanning before treatment; groups were randomized according to clinical severity.

A Canadian study documented full recovery of grade 3 frostbite when iloprost was started within 48 h of injury in 2 long distance runners.[72] In a Finnish study, iloprost was partially beneficial with digit salvage rate of 78% in 4 persons: 2 with contraindication for tPA, 1 with failed tPA therapy, and 1 with vasospasm without thrombosis on angiography.[55] One patient with minimal response to tPA had complete reperfusion with iloprost.

Despite the limitations of these initial studies, iloprost has shown consistently favorable effects.[73] Extending the treatment window, Pandey et al[74] reported good results with iloprost therapy up to 72 h after injury. In 5 Himalayan climbers with 34 digits at risk, 5 d of daily iloprost infusion produced excellent outcomes in 4 of 5 patients. Treatment delayed beyond 72 h has not been beneficial except in 1 patient.[74,75] No serious side effects have been noted in these studies.

Intravenous iloprost should be considered first-line therapy for grade 3 and 4 frostbite <72 h after injury, when tPA is contraindicated, and in austere environments where tPA infusion is considered risky or evacuation to a treatment facility will be delayed. Field use of both iloprost and IV tPA has been advocated to reduce delay in treatment for mountaineers who will invariably take >48 h for evacuation to a hospital.[50] In these situations, iloprost may be the safer alternative. The IV form of iloprost is not approved by the US Food and Drug Administration, however. Consider iloprost for deep frostbite to or proximal to the proximal interphalangeal joint; within 48 h after injury, especially if angiography is not available; or with contraindications to thrombolysis. Expedition physicians should consider adding iloprost to their medical armamentarium, especially if it can be safely sourced and when treatment is occurring outside of the United States. ***Recommendation Grade:*** 1B.

Method of administration

Iloprost dosage is given IV via controlled infusion or syringe pump. Iloprost is mixed with normal saline or dextrose in water. On days 1 through 3, start at an initial rate of 0.5 $ng \cdot kg^{-1} \cdot min^{-1}$, then gradually increase by 0.5 $ng \cdot kg^{-1} \cdot min^{-1}$ at 30-min intervals to a maximum dose of 2.0 $ng \cdot kg^{-1} \cdot min^{-1}$. If intolerable side effects (nausea, headache, flushing) emerge or blood pressure or heart rate are outside normal limits, reduce the rate by 0.5 $ng \cdot kg^{-1} \cdot min^{-1}$ until side effects are tolerable or vital signs normalize. Mild and tolerable side effects can be treated symptomatically, whereas hypotension or severe symptoms require dose reduction. Continue the highest dose achieved or a maximum of 2.0 $ng \cdot kg^{-1} \cdot min^{-1}$ for 6 h total. For days 4 through 5, start directly at the highest/optimum rate or a maximum of 2.0 $ng \cdot kg^{-1} \cdot min^{-1}$ for 6 h daily.[51] Some protocols recommend up to 8 d of treatment; the first dose is considered the most important.

HEPARIN

No evidence supports use of low molecular weight heparin or unfractionated heparin for initial management of frostbite in the field or hospital, although climbers and practitioners in many regions use these medications. Evidence supports use of heparin as adjunctive therapy in tPA protocols, as described previously. Heparin has been used in conjunction with iloprost as well; the 5 patients in the 1994 Groechenig iloprost study,[71] the 1 Israeli traveler with excellent outcome in the Kathmandu study,[74] and 4 patients in the Finnish study[55] were treated with low molecular weight heparin (enoxaparin) in addition to iloprost. Whether low molecular weight heparin offers additional benefit when combined with iloprost requires further investigation; currently data are insufficient for a recommendation on this combination. ***Recommendation Grade:*** Not recommended as monotherapy owing to insufficient data.

OTHER VASODILATOR THERAPY

Vasodilators, such as prostaglandin E_1,[76] nitroglycerin,[46] pentoxifylline,[77,78] phenoxybenzamine, nifedipine, reserpine,[79,80] and buflomedil,[53,81,82] have been used as primary and adjunctive therapies for treatment of frostbite. In addition to vasodilation, some of these agents might also prevent platelet aggregation and microvascular occlusion. Sheridan et al[46] recommend intra-arterial infusion of nitroglycerin during angiography before tPA infusion. A study in rabbits that did not undergo rapid rewarming found benefit from intra-arterial administration of prostaglandin E1.[76] Buflomedil is an alpha-adrenolytic agent that is used widely in Europe with preliminary and anecdotal evidence of good results[53,82]; however, animal models have not replicated these findings.[81] This medication is not approved by the US Food and Drug Administration. Intra-arterial reserpine studied in a controlled trial was found not to be effective.[79]

Pentoxifylline, a methylxanthine-derived phosphodiesterase inhibitor, has been widely used for treatment of peripheral vascular disease and yielded promising results in animal[78,83,84] and human frostbite.[77] Hayes et al[77] recommend pentoxifylline in the controlled-release form of one 400 mg tablet 3 times a day with meals, continued for 2 to 6 wk. Controlled studies of pentoxifylline in management of frostbite have not been performed.

Certain vasodilators have the potential to improve outcomes and can be used with minimal risk. However, as discussed earlier, data demonstrating benefit are limited. Iloprost is the only vasodilator with reasonable scientific evidence supporting its use.

For a summary of the suggested approach to hospital or advanced field clinic treatment of frostbite, see Table 2.

Other post-thaw medical therapy

Once the patient has received initial frostbite therapy, long-term management is initiated to reduce long-term sequelae. Therapeutic options for frostbite after thawing include the following:

HYDROTHERAPY

Daily or twice-daily hydrotherapy at 37 to 39°C (98.6 to 102.2°F) has been recommended in the post-thaw period.[32,34–36,85] Hydrotherapy theoretically increases circulation, removes superficial bacteria, and debrides devitalized tissue.[38] No trials support improved outcomes, but the practice has few negative consequences and has the potential to benefit recovery. Data are insufficient to recommend specific temperature, timing, or duration of therapy. ***Recommendation Grade:*** 1C.

HYPERBARIC OXYGEN THERAPY

Many types of nonfrostbite wounds show accelerated or more complete healing as a result of increased tissue oxygenation from hyperbaric oxygen therapy (HBOT).[86] Because oxygen under pressure increases oxygen tension in the blood, HBOT is typically effective only if blood supply to distal tissues is competent and, therefore, may not be successful in frostbite. However, HBOT may have other effects such as making erythrocytes more malleable and decreasing bacterial load. Despite anecdotal success in extremely limited case series,[87–90] controlled studies have not been conducted. The time, expense, and availability of HBOT also limit its use. At this time, data are insufficient to recommend HBOT for frostbite treatment.

Table 2. Summary of initial hospital management of frostbite

1. Treat hypothermia or serious trauma.
2. Rapidly rewarm in water heated and maintained between 37 and 39°C (98.6 and 102.2°F) until area becomes soft and pliable to the touch (approximately 30 min).
3. Ibuprofen (12 $mg \cdot kg^{-1}$ per day divided twice daily).
4. Pain medication (eg, opiate) as needed.
5. Tetanus prophylaxis.
6. Air dry (ie, do not rub at any point).
7. Debridement: selectively drain (eg, by needle aspiration) clear blisters and leave hemorrhagic blisters intact.
8. Topical aloe vera every 6 h with dressing changes.
9. Dry, bulky dressings.
10. Elevate the affected body part if possible.
11. Systemic hydration.
12. Thrombolytic therapy: consider for deep frostbite at the distal interphalangeal joint or proximal if less than 24 h after thawing; use angiography for prethrombolytic intervention and monitoring of progress. Consider intravenous thrombolysis if angiography is not available.
13. Iloprost therapy: consider for deep frostbite to or proximal to the proximal interphalangeal joint, within 48 h after injury, especially if angiography is not available or with contraindications to thrombolysis.
14. Clinical examination (plus angiography or technetium-99 bone scan if necessary) to assist determination of surgical margins. Evaluation by an experienced surgeon for possible intervention.

Recommendation Grade: Not recommended owing to insufficient data.

SYMPATHECTOMY

Because blood flow is partly determined by sympathetic tone, chemical or surgical sympathectomy has been proposed in the immediate postexposure phase to reduce tissue loss. In a rat lower limb model, early surgical denervation (within 24 h of exposure) reduced tissue loss but had no effect if performed after 24 h.[91] In a rabbit ear model, procaine-induced sympathectomy had no demonstrable beneficial effect.[92] Frostbite patients often experience long-term delayed symptoms, such as pain, paresthesia, and numbness. Chemical or surgical sympathectomy to treat these symptoms has been performed with variable results. In some studies, surgical sympathectomy has been found to reduce duration of pain and expedite demarcation of tissue necrosis. However, it has not been found to reduce the ultimate extent of tissue loss.[41,93] Acute treatment success with IV guanethidine has been reported[94] but was not beneficial in another case report.[95] Sympathectomy may have a role in preventing certain long-term sequelae of frostbite such as pain (putatively caused by vasospasm), paresthesia, and hyperhidrosis.[96,97] Despite many years of study, the data on surgical sympathectomy are limited and conflicting; therefore, a recommendation for their use cannot be made. ***Recommendation Grade:*** Not recommended owing to insufficient data.

HOSPITALIZATION

Hospital admission and discharge are determined on an individual basis. Factors should include severity of the injury, coexisting injuries, comorbidities, and need for hospital-based interventions (tPA, vasodilators, surgery) or supportive therapy, as well as ease of access to appropriate community medical and nursing support. Significant swelling should prompt evaluation for compartment syndrome and admission for observation. Patients with superficial frostbite can usually be managed as outpatients or with brief inpatient stays followed by wound care instructions. Initially, deep frostbite should be managed in an inpatient setting. ***Recommendation Grade:*** 1C.

FASCIOTOMY

Thawing results in reperfusion of ischemic tissue and, in turn, sometimes results in elevated pressures within closed soft-tissue compartments. Compartment syndrome clinically manifests as tense, painful distention with reduced movement and sensation. Urgent attention is necessary to evaluate compartment pressures. If elevated compartment pressures are present, prompt surgical decompression is indicated for limb salvage.[20] ***Recommendation Grade:*** 1C.

SURGICAL TREATMENT OR AMPUTATION

After frostbite occurs, complete demarcation of tissue necrosis may take 1 to 3 mo. Angiography, technetium-99 bone scan, or magnetic resonance imaging may be used to assist determination of surgical margins[42,64,98] in conjunction with clinical findings. If the patient exhibits signs and symptoms of sepsis attributed to infected frostbitten tissue, amputation should be performed expeditiously.[85] Otherwise, amputation should be delayed until definitive demarcation occurs. The affected limb is often insensate. Therefore, an approach that addresses footwear and orthotics is essential to provide optimal function. Our experience has found that early involvement of a multidisciplinary rehabilitation team produces better long-term functional results. Telemedicine or electronic consultation with a surgical frostbite expert to guide local surgeons should be considered when no local expert is available. Because significant morbidity may result from unnecessary or premature surgical intervention, a surgeon with experience evaluating and treating frostbite should assess the need for and the timing of any amputation. ***Recommendation Grade:*** 1C.

Conclusions

This summary provides evidence-based guidelines for prevention and treatment of frostbite. Many important questions remain and should serve as a focus for future research. This includes elucidation of pathophysiology, medications to assist in the prevention of frostbite, perithawing procedures to reduce injury and decrease morbidity, and post-thaw therapies that might improve long-term outcomes.

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Supplementary materials

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