

WILDERNESS MEDICAL SOCIETY PRACTICE GUIDELINES

# Wilderness Medical Society Practice Guidelines for the Prevention and Treatment of Frostbite

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The Wilderness Medical Society convened an expert panel to develop a set of evidence-based guidelines for the 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 based on the quality of supporting evidence and balance between the benefits and risks/burdens for each modality according to methodology stipulated by the American College of Chest Physicians.

*Key words:* frostbite, frostbite prevention, hypothermia, rewarming, aloe vera, thrombolysis

## 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 disseminate knowledge about best practice 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 based on the quality of supporting evidence and balance between the benefits and risks/burdens for each modality. We then provide suggested approaches for prevention and management that incorporate these recommendations.

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## Methods

The expert panel was convened at the 2010 Annual Winter Meeting of the WMS in Park City, Utah. Members were selected based on their clinical and/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 (ACCP) statement on grading recommendations and strength of evidence in clinical guidelines (Table 1).<sup>1</sup>

**Table 1.** ACCP classification scheme for grading evidence in clinical guidelines

<i>Grade</i>	<i>Description</i>	<i>Benefits vs Risks and Burdens</i>	<i>Methodological Quality of Supporting Evidence</i>
1A	Strong recommendation, high-quality evidence	Benefits clearly outweigh risks and burdens or vice versa	RCTs without important limitations or overwhelming evidence from observational studies
1B	Strong recommendation, moderate-quality evidence	Benefits clearly outweigh risks and burdens or vice versa	RCTs with important limitations or exceptionally strong evidence from observational studies
1C	Strong recommendation, low-quality or very low-quality evidence	Benefits clearly outweigh risks and burdens or vice versa	Observational studies or case series
2A	Weak recommendation, high-quality evidence	Benefits closely balanced with risks and burdens	RCTs without important limitations or overwhelming evidence from observational studies
2B	Weak recommendation, moderate-quality evidence	Benefits closely balanced with risks and burdens	RCTs with important limitations or exceptionally strong evidence from observational studies
2C	Weak recommendation, low-quality or very low-quality evidence	Uncertainty in the estimates of benefits, risks and burden; benefits, risk and burden may be closely balanced	Observational studies or case series

RCT, randomized controlled trial.

### Pathophysiology of Frostbite

The freezing injury of frostbite 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, but does not involve actual ice crystal formation. Neuronal cooling and ischemia produces hyperesthesia or paresthesia. In the freeze-thaw phase, ice crystals form intracellularly (during a more rapid-onset freezing injury) and/or extracellularly (during a slower freeze), causing protein and lipid derangement, cellular electrolyte shifts, cellular dehydration, cell membrane lysis and cell death.<sup>2</sup> The thawing process may initiate ischemia-reperfusion injury and the inflammatory response. In the vascular stasis phase, vessels may fluctuate between constriction and dilation; blood may leak from vessels or coagulate within them.<sup>3-5</sup> The late ischemic phase results from progressive tissue ischemia and infarction from a cascade of events including: inflammation mediated by thromboxane A<sub>2</sub>, prostaglandin F<sub>2</sub>-alpha, bradykinins, and histamine; intermittent vasoconstriction of arterioles and venules; continued reperfusion injury; showers of emboli coursing through the microvessels;<sup>6,7</sup> and thrombus formation in larger vessels.<sup>8</sup> Destruction of the microcirculation is the main factor leading to cell death.<sup>9</sup> The initial cellular damage caused by ice crystals and the subsequent post-thawing

processes are made worse if refreezing follows thawing of injured tissues.<sup>10,11</sup>

### Classification of Frostbite

Frostbite has been divided into 4 tiers or “degrees” of injury, historically following the classification scheme for thermal burn injury. These classifications are based on *acute physical findings* and *advanced imaging after rewarming*.<sup>12</sup> These categories can be difficult to assess in the field and before rewarming, since the still-frozen tissue is hard, pale, and anesthetic. An alternate 2-tiered classification which is more appropriate for field use is suggested below after the 4-tier classification.

*Frostnip* is distinct from frostbite but may precede it. Frostnip is a superficial non-freezing cold injury associated with intense vasoconstriction on exposed skin, usually cheeks, ears, or nose. Ice crystals, appearing as frost, form on the surface of the skin. By definition, ice crystals do not form in the tissue nor does tissue loss occur in frostnip. The numbness and pallor resolve quickly after covering the skin with appropriate clothing, warming the skin with direct contact, breathing with cupped hands over the nose, or gaining shelter that protects from the elements. No long-term damage occurs. The appearance of frostnip signals conditions favorable for frostbite and

appropriate action should be undertaken immediately to prevent injury.

*First-degree frostbite* presents with numbness and erythema. A white or yellow firm, 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 results in superficial skin vesiculation; a clear or milky fluid is present in the blisters, surrounded by erythema and edema.

*Third-degree frostbite* creates deeper hemorrhagic blisters, indicating that the injury has extended into the reticular dermis and beneath the dermal vascular plexus.

*Fourth-degree frostbite* injury extends completely through the dermis and involves the comparatively avascular subcutaneous tissues, with necrosis extending into muscle and to the level of bone.

To simplify classification, either in the field or before rewarming and/or imaging, we favor the following 2-tier classification scheme:

- *Superficial* no or minimal anticipated tissue loss, corresponding to 1st- and 2nd-degree injury
- *Deep* deeper injury and anticipated tissue loss, corresponding to 3rd- and 4th-degree injury

Severity of frostbite may vary within a single extremity.

## Prevention

The adage that “prevention is better than treatment” is especially true for frostbite, which is typically preventable and often not improved by treatment. Risk of frostbite can also be related to underlying medical problems, and 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 = heat). One must both ensure adequate perfusion and minimize heat loss to prevent frostbite.

*Maintaining peripheral perfusion* Preventive measures to ensure local tissue perfusion include: 1) maintaining adequate core temperature and body hydration; 2) minimizing effects of known diseases and/or medications/drugs that may decrease perfusion; 3) covering all skin and the scalp to avoid vasoconstriction; 4) minimizing restriction in blood flow, such as constrictive clothing, footwear, or immobility; 5) ensuring adequate nutrition; 6) using supplemental oxygen in severely hypoxic conditions (eg, over 7500 m). Recommendation Grade: 1C.

*Exercise* Exercise is a specific method to maintain peripheral perfusion because it enhances the level and frequency of cold-induced peripheral vasodilation. In

one small study, exercise resulted in cold-induced peripheral vasodilation in the toes of 58% of subjects vs only 28% in controls who had not exercised.<sup>13</sup> Another study showed an increase in thermal response in the hands during exercise.<sup>14</sup> Using exercise to increase warmth can lead to exhaustion, however, with profound systemic heat loss upon collapse. 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 with a risk of frostbite, specifically below  $-15^{\circ}\text{C}$  even with low wind speeds;<sup>15</sup> 2) protecting skin from moisture, wind and cold; 3) avoiding perspiration or wet extremities; 4) increase insulation and skin protection by layering clothes appropriately; 5) ensuring the appropriate behavioral response to changing environmental conditions (eg, not being under the influence of drugs and/or alcohol or extreme hypoxemia);<sup>16</sup> 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 constrict flow if used within a boot); 7) performing “cold checks” if an individual experiences extremity numbness or pain or is concerned that frostbite may be developing; 8) recognition of frostnip or superficial frostbite before it becomes more serious; and 9) minimizing duration of cold exposure. Emollients do not protect against—and may even increase—the risk of frostbite.<sup>17</sup> The time period that a digit or extremity can remain numb before developing frostbite is unknown; thus, paresthesia should be addressed as soon as possible. An extremity at risk for frostbite (eg, numb, poor dexterity, pale color) should be warmed with adjacent body heat from the person or a companion, in the axilla, or on the abdomen. Measures should be taken to protect the skin from the cold in order to prevent frostbite. 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 extraneous material from the body part. Do not rub or apply ice or snow to the affected area.<sup>18</sup>

*Refreezing injury* A decision must be made whether or not to thaw the tissue. If environmental conditions are such that thawed tissue could re-freeze, it is safer to keep the affected part frozen until a thawed state can be maintained. The prostaglandin and thromboxane release associated with the freeze-thaw cycle<sup>18-20</sup> causes vaso-

constriction, platelet aggregation, thrombosis and, ultimately, cellular injury. Refreezing thawed tissue further increases these mediators, and significant morbidity may result. One must absolutely avoid refreezing if field-thawing occurs. Recommendation Grade: 1B.

*Spontaneous/passive thawing* Most frostbite will thaw spontaneously and should be allowed to do so if rapid rewarming cannot be readily achieved. Do not purposefully keep tissue below freezing temperatures, as it will increase the duration that the tissue is frozen and could easily result in more proximal freezing and higher 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 below.

### **Scenario 1: The Frozen Part Has the Potential of Re-freezing and Will Not Be Actively Thawed**

### **Scenario 2: The Frozen Part Can Be Kept Thawed and Warm With Minimal Risk of Refreezing Until Evacuation is Completed**

## THERAPEUTIC OPTIONS FOR BOTH SCENARIOS

Many of these guidelines parallel the State of Alaska Cold Injuries Guidelines.<sup>21</sup> Therapeutic options include the following:

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

*Hydration* Vascular stasis can result from frostbite injury. No studies have specifically examined outcomes relating hydration status to frostbite, but it is believed that appropriate hydration and avoidance of hypovolemia are important in frostbite recovery, and fluids should be administered if possible. Oral fluids should be given if the patient is alert and has no gastrointestinal symptoms. If the patient is nauseous, vomiting, or has an altered mental status, IV normal saline should be given if available. Intravenous fluids should be warmed before infusion, if possible, and should be infused in small boluses since slower infusion will result in fluid cooling as it passes through the IV tubing. Volume status should be optimized if the patient shows evidence of clinical dehydration. Recommendation Grade: 1C.

*Low molecular weight dextran* Intravenous low molecular weight dextran (LMWD) has been shown to

decrease blood viscosity by preventing red blood cell aggregation and the formation of microthrombi and can be given in the field. In some animal studies, the extent of tissue necrosis was found to be significantly less than in controls when LMWD was used<sup>22-25</sup> and is more beneficial if given early.<sup>26</sup> In one animal trial,<sup>27</sup> tissue in the LMWD group thawed slightly more rapidly but overall tissue loss was not different than controls. The medication package insert recommends a test dose prior to administration because of a low risk of anaphylaxis. The slight risk of bleeding is minimal and benefits seem to outweigh this risk; however, availability is limited in the United States. Low molecular weight dextran has not been evaluated in combination with other treatments such as thrombolytics. Low molecular weight dextran should be given if available and the patient is not being considered for other systemic treatments such as thrombolytic therapy. Recommendation Grade: 2C.

*Ibuprofen* Non-steroidal anti-inflammatory medications (NSAIDs) block the arachidonic pathway and decrease production of prostaglandins and thromboxanes.<sup>28</sup> These mediators can lead to vasoconstriction, dermal ischemia, and further tissue damage. No studies have directly demonstrated that any particular anti-inflammatory agent or dosing is clearly beneficial to outcome. Aspirin has been proposed as an alternative and is used in many parts of the world for anti-inflammatory and platelet inhibition effects. One rabbit ear model study showed a 23% tissue survival with aspirin vs control.<sup>29</sup> However, aspirin theoretically blocks the production of certain prostaglandins that are beneficial to wound healing,<sup>30</sup> and the authors of the rabbit ear model study even recommend ibuprofen in their treatment algorithm. No studies specifically compare aspirin to ibuprofen in frostbite. If available, ibuprofen should be started in the field at a dose of 12 mg/kg per day divided twice daily (minimum to inhibit harmful prostaglandins<sup>28</sup>) to a maximum of 2400 mg/day divided four times daily if the patient is experiencing pain. Recommendation Grade: 2C.

## SPECIFIC RECOMMENDATIONS—SCENARIO 1

Therapeutic options for frostbite in Scenario 1 include the following:

*Dressings* There is no evidence to support the idea that applying a dressing to a frostbitten part that is intended to remain frozen until rewarming can safely be achieved. If this is considered, it should only be done if it is practical to do so 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 using the frozen extremity for mobility is considered, a risk/benefit analysis must consider the potential for further trauma and possible poorer outcomes. While 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, however, and was based on the panel's opinion. Mills described frostbite patients who ambulated on frozen extremities for days and sustained no or limited amputation.<sup>31</sup> 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. Measures should be taken to protect frozen tissue to prevent further trauma. Recommendation Grade: 1C.

## SPECIFIC RECOMMENDATIONS—SCENARIO 2

Therapeutic options for frostbite in Scenario 2 include the following:

*Rapid field rewarming of frostbite* Field rewarming by warm water bath immersion can and should be performed if the proper equipment and methods are available and definitive care is more than 2 hours away. Other heat sources (eg, fire, space heater, oven) should be avoided because of the risk of thermal injury. Rapid rewarming by water bath has been shown to result in better outcomes than slow rewarming.<sup>18,25,32</sup> 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°C to 39°C (98.6–102.2°F) using a thermometer to maintain this range.<sup>33</sup> 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 seconds 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.<sup>34,35</sup> Because the water may cool quickly after the rewarming process is started, the water should be continually, but carefully, warmed to the target temperature with close monitoring by thermometer or a subjective determination with the caregiver's hand. The tissue is often numb, so correct temperature is vital to avoid iatrogenic injury resulting in further damage to tissue. If the frozen part is being rewarmed in a pot, care must be taken that the frozen part does not touch the sides, to prevent damage to the skin. Rewarming is complete when the involved part takes on a red/purple appearance and becomes soft and pliable to the touch. This result is usually accomplished

in approximately 30 minutes but may take a longer or shorter amount of time depending on the extent and depth of the injury. The affected tissues should then be allowed to air dry or gently dried with blotting motions to minimize further damage. Under appropriate circumstances, the method of field rewarming described above is the first definitive step in frostbite treatment. Recommendation Grade: 1B.

*Antiseptic solution* Adding an antiseptic solution (eg, povidone-iodine, chlorhexidine) to the rewarming water has theoretical benefits of reducing bacteria on the skin. However, this practice is not substantiated by supporting evidence in frostbite care. Frostbite is not an inherently infectious process and most injuries do not become infected. If available, adding an antiseptic solution to the water while rewarming is unlikely to be harmful and may reduce the risk of cellulitis if severe edema is present in the affected extremity. Recommendation Grade: 2C.

*Pain control* During rewarming, pain medications (eg, NSAIDs or opiate analgesics) should be given to control symptoms as dictated by individual patient response and medication availability. Recommendation Grade: 1C.

*Spontaneous/passive thawing* According to the above guidelines, rapid rewarming is strongly recommended. If field rewarming is not possible, however, spontaneous or slow thawing may be unavoidable and should be allowed. Slow rewarming can be accomplished by moving into a warmer location (eg, tent or hut) and warming with adjacent body heat from the patient or a caregiver (eg, axilla or abdomen). Although rapid rewarming should be undertaken when possible, 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 an evacuation, aspiration of the blister and application of a dry gauze dressing should be performed in the field to minimize infection. Hemorrhagic bullae should not be aspirated or debrided electively in the field. These recommendations are common practice but lack evidence beyond case series.<sup>29</sup> Blisters should be evaluated to determine whether they pose a risk for rupture and/or infection and aspirated according to the above guidelines. Recommendation Grade: 2C.

*Topical aloe vera* Aloe vera ointment has been shown in an observational study<sup>36</sup> and an animal model<sup>29</sup> to improve frostbite outcome by reducing prostaglandin and thromboxane formation. Topical agents do not penetrate far into tissues, however, and aloe vera is theoretically only beneficial for superficially injured areas. In addition, the study supporting aloe vera's benefit exam-

ined its application on unroofed blebs where it would be able to penetrate underlying tissue. However, risks associated with application of aloe vera are low. If available, topical aloe vera should be applied to thawed tissue prior to applying dressings. Recommendation Grade: 2C.

**Dressings** Bulky, dry gauze dressings should be applied to the frozen parts for protection and wound care. Substantial edema should be anticipated and 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 again consider the potential for further trauma and, ultimately, higher morbidity if a thawed part is used for ambulation. For example, it would be reasonable to walk on a foot with thawed toes for evacuation purposes but inadvisable to walk on a recently thawed frostbitten foot because of the potential resulting morbidity. After the rewarming process, swelling should be anticipated. Boots (or inner boots) may need to be worn continually to compress swelling. Boots that are removed may not be able to be replaced if walking or climbing is absolutely necessary in order to self-evacuate. 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.<sup>36,37</sup> Recommendation Grade: 1C.

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

**Oxygen** The recovery of thawed tissue partly depends on the level of tissue oxygenation in the post-freezing period. Although evidence is lacking to support the use of supplemental oxygen in frostbite, oxygen (if available) may be delivered by face mask or nasal cannula if the patient is hypoxic (oxygen saturation < 90%) or the patient is at high altitude above 4000 m. Recommendation Grade: 2C.

Summary of suggested approach to the field treatment of frostbite: see Table 2.

### 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/field clinic, potential therapeutic options for frostbite include:

**Treatment of hypothermia** Similar recommendations apply to the hospital/field clinic treatment of hypother-

**Table 2.** Summary of field treatment of frostbite (over 2 hrs from definitive care)

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

mia prior to frostbite treatment (see above). Recommendation Grade: 1C.

**Hydration** Similar recommendations apply in the hospital/field clinic regarding hydration. Recommendation Grade: 1C.

**Low molecular weight dextran** Similar recommendations apply in the hospital/field clinic regarding LMWD. Recommendation Grade: 2C.

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

**Debridement of blisters** Clear or cloudy blisters contain prostaglandins and thromboxanes that may damage underlying tissue. Hemorrhagic blisters are thought to signify deeper tissue damage into the dermal vascular plexus. Common practice is to selectively drain clear blisters (eg, by needle aspiration) while leaving hemorrhagic blisters intact.<sup>35-39</sup> While this selective debridement 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 may lead to the desiccation of exposed tissue, and that blisters should only be removed if they are tense, likely to be infected, or interfere with the patient's range of motion.<sup>40</sup> Debridement or aspiration of clear, cloudy, or tense blisters may be at the discretion of the treating provider, with consideration of

patient circumstances, until better evidence is available. Recommendation Grade: 2C.

*Topical aloe vera* Topical aloe vera cream or gel should be applied to the thawed tissue prior to applying dressings. Aloe vera cream or gel can be reapplied at each dressing change, or every 6 hours.<sup>36</sup> 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, based on the idea that edema increases the skin's susceptibility to infection by gram-positive bacteria.<sup>37</sup> 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 lower dose of 12 mg/kg divided twice daily (to inhibit harmful prostaglandins but remain safer on the gastrointestinal system<sup>28</sup>) until the frostbite wound is healed or surgical management occurs (typically 4-6 weeks). Recommendation Grade: 2C.

*Thrombolytic therapy* The goal of thrombolytic therapy in frostbite injury is to address microvascular thrombosis. For deep frostbite injury with potential significant morbidity, angiography and use of either IV or intra-arterial tissue plasminogen activator (tPA) within 24 hours of thawing may salvage some or all tissue at risk. The retrospective, single-center review by Bruen et al<sup>41</sup> demonstrated a reduction in digital amputation rates from 41% in those patients that did not receive tPA to 10% in those patients receiving tPA within 24 hours of injury. The 20-year series presented by the Regions Hospital group showed that two-thirds of those who received intra-arterial tPA responded well and that the amputation rate correlated closely with angiographic findings.<sup>42</sup> The Massachusetts General Hospital group has proposed a screening and treatment tool for thrombolytic management of frostbite based upon a case report and their evaluation of the Utah and Minneapolis experiences.<sup>43</sup> Twomey et al from Hennepin County Medical Center have developed a specific protocol based on a small group of good outcomes with tPA.<sup>44</sup> Animal studies demonstrate benefit from thrombolytics as well.<sup>45</sup>

When considering thrombolytics, a risk/benefit analysis should be performed by a physician with experience

in the use of thrombolytics in frostbite. Only deep injuries with potential for significant morbidity (eg, extending proximally to the proximal interphalangeal joints of the digits) should be considered for thrombolytic therapy. The 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 also not been evaluated.

Thrombolytic treatment should be undertaken in a facility 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 could be started within 24 hours of the injury thawing. Use of tPA in the field setting is not recommended because it may be impossible to detect and treat bleeding complications. Published protocols include the use of heparin in conjunction with thrombolytic therapy to prevent recurrent local thrombosis<sup>43,46,47</sup> and heparin is recommended in this circumstance as adjunctive therapy. Angiography or pyrophosphate scanning should be used to evaluate the initial injury and monitor progress after tPA administration as directed by local protocol and resources (angiography scanning for intra-arterial, and pyrophosphate scanning for IV). The 3 published reports<sup>41,43,44</sup> include a total of only 52 patients, and the published abstract from Regions hospital<sup>42</sup> included 66.

A recent randomized trial assessed the efficacy of aspirin plus: (1) buflomedil, (2) iloprost, and (3) intravenous tPA plus iloprost.<sup>48</sup> Forty-seven patients with severe frostbite, with 407 digits at risk, were randomized to 8 days of treatment with the 3 different regimens. Iloprost alone was found superior to buflomedil and to tPA plus iloprost. The authors suggest, however, that certain patients may benefit from the combined treatment of tPA and iloprost. 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 hours of injury as a reasonable choice in a proper facility. Recommendation Grade for thrombolytic therapy: 1C.

*Imaging* In patients with delayed presentation (greater than 24 hours from the time of the frostbite thawing), non-invasive imaging with technetium pyrophosphate<sup>12</sup> or MRA<sup>49</sup> can be used at an early stage to predict the likely levels of tissue viability for amputation. Cauchy<sup>12</sup> described the use of the combination of a simple clinical scoring system and technetium scanning to successfully predict the subsequent level of amputation on day 2 after frostbite rewarming. If available, appropriate imaging should be used to assess tissue viability and guide timing and extent of amputation. Recommendation Grade: 1C.

**Heparin** No evidence supports the 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 do employ these medications. Evidence supports the use of heparin as adjunctive therapy in a tPA protocol as described above. Recommendation Grade: Not recommended as monotherapy due to insufficient data.

**Vasodilator therapy** Vasodilators, such as prostaglandin E1 (PGE1),<sup>50</sup> the prostacyclin analogue iloprost,<sup>51,52</sup> nitroglycerin,<sup>43</sup> pentoxifylline,<sup>53,54</sup> phenoxymethylamine, nifedipine, reserpine,<sup>55,56</sup> and buflomedil<sup>48,57,58</sup> have been used as primary and adjunctive therapies in the treatment of frostbite injuries. In addition to vasodilatation, some of these agents may also prevent platelet aggregation and microvascular occlusion that occur after frostbite. Sheridan et al recommend intra-arterial infusion of nitroglycerin during angiography, prior to t-PA infusion.<sup>43</sup> A study in rabbits that did not undergo rapid rewarming showed some benefit from intra-arterial administration of PGE1.<sup>50</sup> Buflomedil is an alpha adrenergic agent that is used widely in Europe with some preliminary and anecdotal evidence of good results;<sup>48,58</sup> however, animal models have not replicated these findings.<sup>57</sup> In addition, the medication is not approved by the Food and Drug Administration in the United States. Intra-arterial reserpine has been studied in a case control study and found not to be effective.<sup>55</sup>

There are limited data from Europe supporting the use of iloprost,<sup>51</sup> and a recent study<sup>48</sup> showed a significant decrease in the rate of digit amputation, prompting the authors to recommend iloprost in severe frostbite injuries. After rapid rewarming and administration of 250 mg of aspirin and 400 mg IV buflomedil, 47 patients with 407 digits at risk were randomized to receive 250 mg aspirin per day, plus either buflomedil, iloprost, or tPA with iloprost. All patients were treated for 8 days. The iloprost group had the lowest overall amputation rate, 0% compared to 16% in the tPA group and 60% in the buflomedil group. The tPA (with iloprost) group started with slightly more severe frostbite, however, and a beneficial effect of tPA could not be ruled out. Intravenous prostacyclin alone could be considered as an alternative if appropriate monitoring facilities are available.

Pentoxifylline, a methylxanthine-derived phosphodiesterase inhibitor, has been widely used in the treatment of peripheral vascular disease and has yielded some promising results in animal<sup>53,59,60</sup> and human frostbite.<sup>54</sup> Hayes<sup>54</sup> recommends pentoxifylline in the controlled-release form of one 400 mg tablet 3 times a day with meals, continued for 2 to 6 weeks. Controlled studies of pentoxifylline in the management of frostbite have yet to be performed.

**Table 3.** Summary of initial hospital management of frostbite

1. Treat hypothermia or serious trauma
2. Rapidly rewarm in water heated and maintained between 37-39°C (98.6-102.2°F) until area becomes soft and pliable to the touch (approximately 30 minutes)
3. Ibuprofen (12 mg/kg 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 hrs 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 with potential significant morbidity if less than 24 hours after thawing; use angiography for pre-thrombolytic intervention and monitoring of progress
13. Clinical examination (plus angiography and/or technetium-99 bone scan if necessary) to assist determination of surgical margins
14. Evaluation by an experienced surgeon for possible intervention

Certain vasodilators have the potential to improve outcomes and can be used with minimal risk. However, as discussed above, the data demonstrating benefit is limited. Iloprost is the only vasodilator with reasonable scientific evidence supporting its use, although it is currently not available in many countries including the United States. Recommendation for prostacyclin/iloprost: 1C.

Summary of suggested approach to hospital/advanced field clinic treatment of frostbite (see Table 3).

### 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:

**Hydrotherapy** Daily or twice daily hydrotherapy at 37°C to 39°C (98.6–102.2°F) has been recommended in the post-thaw period.<sup>32,34-36,61</sup> Hydrotherapy theoretically increases circulation, removes superficial bacteria, and debrides devitalized tissue.<sup>37</sup> There are no trials to 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 non-frostbite wounds show accelerated or more complete healing as a result of increased tissue oxygenation from hyperbaric oxygen therapy.<sup>62</sup> Since oxygen under pressure increases the oxygen tension in the blood, hyperbaric therapy is typically effective only if the blood supply to the distal tissues is competent and, therefore, may not be successful in frostbite. However, hyperbaric therapy may have other effects such as making erythrocytes more malleable and decreasing bacterial load. Despite anecdotal success in extremely limited case series,<sup>63-65</sup> controlled studies have not been conducted. The time, expense, and availability of hyperbaric therapy also limit its use. At this time, data are insufficient to recommend hyperbaric oxygen therapy for treatment of frostbite. Recommendation Grade: Not recommended due to insufficient data.

*Sympathectomy* Since blood flow is partly determined by sympathetic tone, chemical or surgical sympathectomy has been proposed in the immediate post-exposure phase to reduce tissue loss. In a rat lower limb model, early surgical denervation (within 24 hours of exposure) reduced tissue loss, but had no effect if performed after 24 hours.<sup>66</sup> In a rabbit ear model, however, a procaine sympathectomy had no demonstrable beneficial effect.<sup>67</sup> Frostbite patients often experience long-term delayed symptoms, such as pain, paresthesias, and numbness. Chemical or surgical sympathectomy to treat these symptoms has been performed with variable results. In some studies, surgical sympathectomy has been shown to reduce duration of pain and expedite demarcation of tissue necrosis. However, it has not been shown to reduce the ultimate extent of tissue loss.<sup>39,68</sup> Acute treatment success with IV guanethidine has been reported<sup>69</sup> but was not beneficial in another case report.<sup>70</sup> Sympathectomy may have a role in preventing some long-term sequelae of frostbite such as pain (often due to vasospasm), paresthesias, and hyperhidrosis.<sup>71,72</sup> Despite many years of study, the data on surgical sympathectomy are limited and conflicting, and a recommendation for their use cannot be made. Recommendation Grade: Not recommended due to insufficient data.

*Hospitalization* Hospital admission and discharge is determined on an individual basis. Factors should include the severity of the injury(s), co-existing injuries, co-morbidities, and the need for hospital-based interventions (tPA, vasodilators, surgery) or supportive therapy, as well as ease of access to appropriate medical and nursing support in the community. Significant swelling should prompt an evaluation for compartment syndrome and admission for observation. Patients with superficial frostbite can usually be managed as outpatients or with brief inpatient stays with specific wound care instruc-

tions. Initially, deep frostbite should be managed in an inpatient setting. Recommendation Grade: 1C.

*Fasciotomy* Thawing will reperfuse ischemic tissue that, in turn, can result in the development of elevated pressures within a closed soft tissue compartment. Compartment syndrome is clinically manifest by tense, painful distension with reduction in movement and sensation. Urgent attention and/or consultation is necessary to evaluate compartment pressures. If elevated compartment pressures are present, urgent surgical decompression is indicated for limb salvage.<sup>18</sup> Recommendation Grade: 1C.

*Surgical treatment/amputation* After frostbite occurs, complete demarcation of tissue necrosis may take 1 to 3 months. Angiography, technetium-99 bone scan and/or magnetic resonance imaging may be used to assist determination of surgical margins<sup>38,49,73</sup> in conjunction with clinical findings. If the patient develops signs and symptoms of sepsis attributed to infected frostbitten tissue, amputation should be performed expeditiously.<sup>61</sup> Otherwise, amputation should be delayed until definitive demarcation occurs, a process that may take weeks to months. The affected limb is often insensate. Consequently, an approach that addresses both protective footwear and orthotics to provide optimal function is essential. Our experience has shown that early involvement of a multidisciplinary rehabilitation team will produce 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. Since 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 amputations. 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. Such research includes potential medications to assist in the prevention of frostbite, specific peri-thawing procedures to reduce injury and decrease morbidity, and post-thaw therapies that could improve the long-term outcomes of frostbite injury.

## Disclosure

None of the authors has any conflict of interest or financial interest to report regarding the material presented in this manuscript.

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