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REVIEW ARTICLE

Reconstructive

Practical Review of the Current Management of Frostbite Injuries

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Summary: Frostbite is an injury that occurs when the skin and tissues are exposed to temperatures below their freezing point. This type of injury can lead to various complications such as functional loss, chronic pain, and psychological trauma. As such, understanding frostbite management is crucial for optimal patient care. A scoping review was conducted in February 2022 using PubMed, EMBASE, referenced articles and snowballing to identify relevant published articled using the terms “frostbite” and “management” and “surgery. Articles related to pathophysiology, classifications, radiography, complications, and medical and surgical management were included to formulate recommendations for practical management. Two hundred fifty-one articles were identified and 54 met inclusion criteria. Rapid rewarming in warm water (40-42 °C) remains the standard of care. Thrombolytic therapy has been shown in numerous studies to improve tissue salvage. Radiographic imaging has become crucial in the evaluation and management in frostbite injury. Current literature recommends delayed surgery with soft tissue debridement and bone scan-guided amputations. Surgical intervention including debridement, selective blister drainage, fasciotomies, surgical salvage, skin grafts, and flaps are often necessary in these patients towards optimizing form and function. The true prevalence and incidence of frostbite injury is unknown. A centralized national database will improve our understanding of the diagnostic and management modalities used in frostbite care. Plastic surgeons have a critical role in the management of frostbite care and must work with an interdisciplinary team to identify the best treatment route for optimal patient care. *(Plast Reconstr Surg Glob Open 2022;10:e4618; doi: 10.1097/GOX.0000000000004618; Published online 24 October 2022.)*

INTRODUCTION

Frostbite injury, once considered a military phenomenon, has become more common in the civilian population, with increased incidence among homeless individuals, industrial workers, and people engaging in cold weather recreational activities.[1–4] Although data on the overall incidence of frostbite are limited, a retrospective study of 241 patients reported a 3% mortality rate. In the same study, however, surgical intervention with debridement and/or amputation was required in 20% of patients.[5] Complications from frostbite injury include local tissue swelling, tissue necrosis, gangrene, compartment syndrome, joint immobility, and contractures, amongst other physical deformities.[6,7]

Improved understanding of the pathophysiology of frostbite has led to the development of various treatment regimens, including the widespread use of whirlpool rapid rewarming, thrombolytic therapy, radiology-guided surgical reconstruction, and long-term pain management.[2,8,9] Although these treatment regimens have decreased frostbite morbidity, there is a paucity of literature detailing the surgical and medical management of frostbite, making treatment guidelines unclear. As frostbite complications can lead to debilitating consequences such as chronic pain and functional impairment, reconstruction is often necessary.[7] The objective of this article is to provide a practical overview of the current medical and surgical management of frostbite to better equip physicians and surgeons with the tools to provide adequate patient care.

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METHODS

A literature search of PubMed and EMBASE databases performed on February 20, 2022 using the terms “frostbite” and “management” and “surgery” found 120 PubMed articles and 111 EMBASE articles. Twenty

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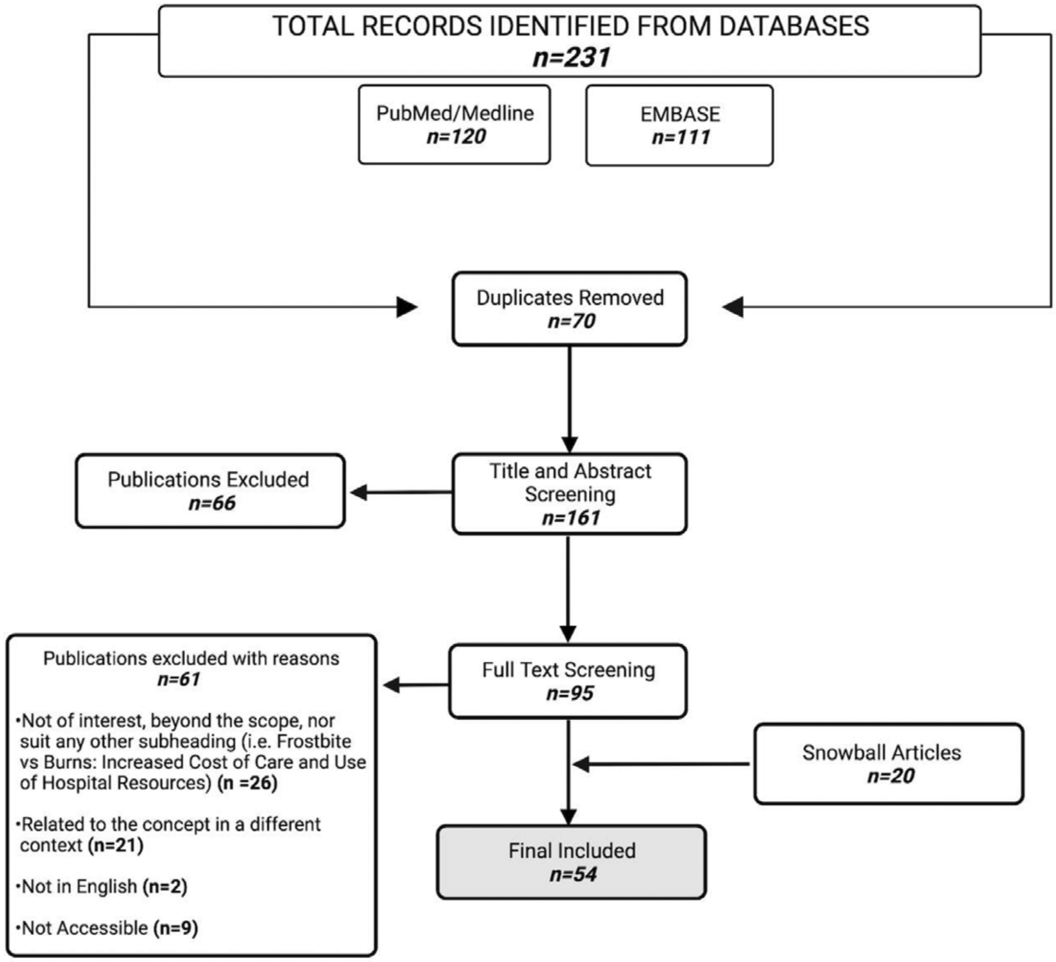

Fig. 1. PRISMA Flow Diagram. PRISMA flow diagram detailing the number of database searches, abstracts screened and full texts articles retrieved to arrive at 54 articles.

additional articles were retrieved from references articles or snowballing (Fig. 1). All duplicates were removed (n = 70). Title and abstracts were screened and articles that did not meet inclusion criteria (n = 66) were removed. Inclusion criteria included articles written in English, published prior to February 20, 2022, and addressed frostbite incidence and management from all evidence levels. Publications that were beyond the scope of this article, animal studies, or those that were not accessible through PubMed or EMBASE (n = 61) were excluded. Full-text data were analyzed (n = 54) for study type and overarching themes and were synthesized to provide a review of the medical and surgical management of frostbite.

RESULTS

Five level-I studies were identified, including a randomized controlled trial involving 47 patients, a meta-analysis of frostbite thrombolytic therapy, an open-label study that involved 19 patients, and two systematic reviews. Three level-II studies were identified: one nonrandomized control trial and two prospective/observational studies. The majority of the articles were classified as level III studies, including retrospective reviews and case reports/series.

Pathophysiology

Frostbite is an injury that occurs when the skin and tissues are exposed to temperatures below their freezing point (approximately –0.53°C).[5,10,11] This intense cold exposure results in peripheral vasoconstriction with intermittent cycles of vasodilation. Consequently, blood is shunted from distal areas of the body, resulting in tissue freezing of the feet (47%), hands (19%), ears, lips, and nose (3%).[10,12]

As the tissue freezes, extracellular ice crystals form, leading to electrolyte and pH imbalances, cellular dehydration, cellular lysis, and microvascular damage. Vasodilation following rewarming triggers the reperfusion injury cascade through the generation of free radicals and production of prostaglandins, thromboxane, bradykinin, and histamines. These vasoactive substances exacerbate endothelial injury, decrease blood flow, and increase thrombosis. Together, these factors eventually lead to tissue ischemia and necrosis.[8–10] Figure 2 describes a schematic of the frostbite pathophysiology.

Patient Presentation

Patients may have initial complaints of paresthesia, clumsiness, and joint stiffness. Appearance of frostbitten

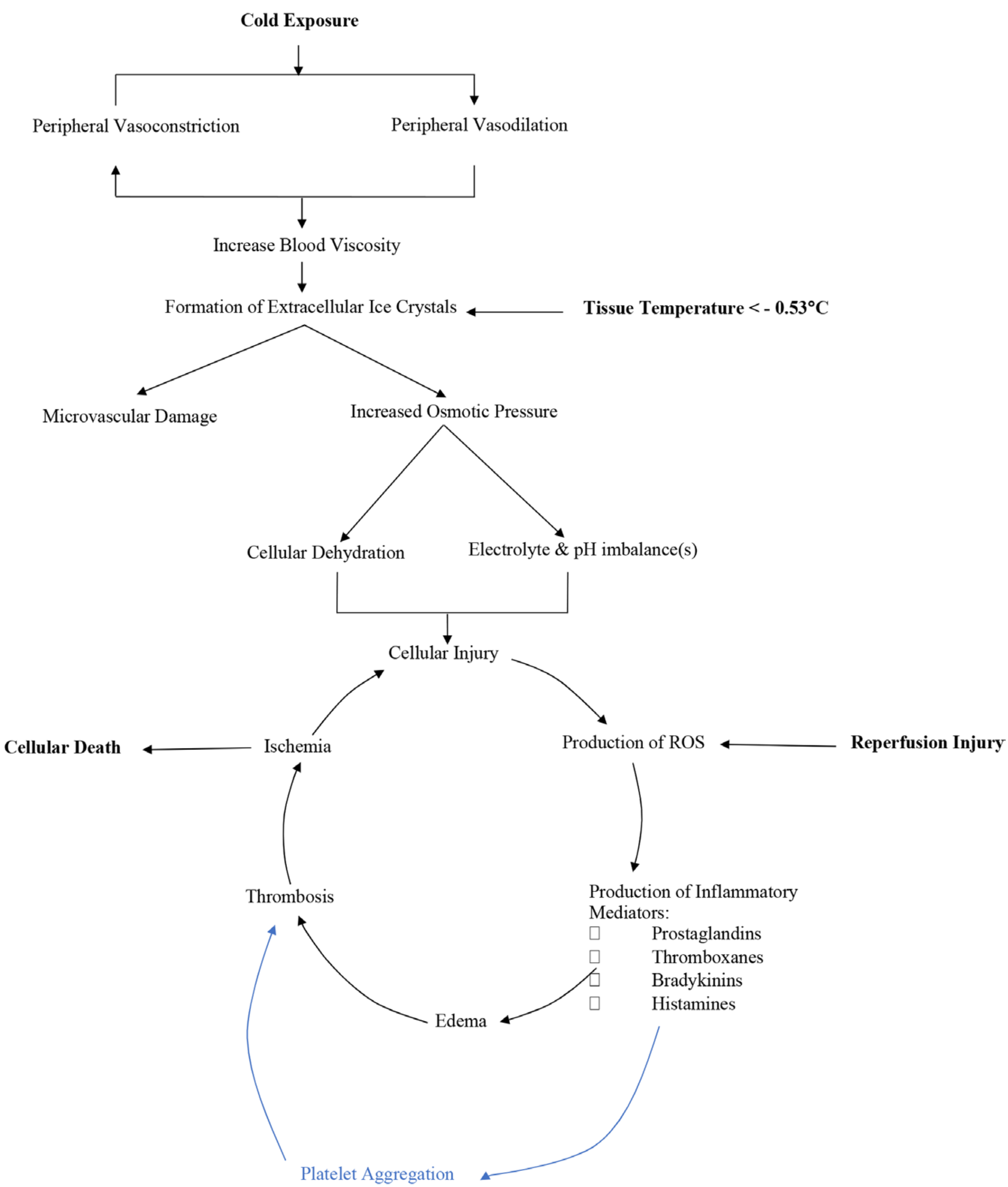

Fig. 2. Frostbite injury pathophysiology adapted from Knapik et al and Murphy et al. Schematic diagram of frostbite injury, which ensues when tissue is exposed to temperatures below −0.53°C, followed by the successive formation of extracellular ice crystals, microvascular damage, inflammation, and eventually cellular death. Abbreviations: ROS, reactive oxygen species.

skin is variable depending on skin tone and may appear yellow, pale/whitish, or mottled blue. Skin may also appear hard or waxy.[2,8,9] After rewarming, affected tissue may appear red and edematous secondary to hyperemia. Clear, yellow, or serosanguinous fluid blisters are typically a later finding and denote favorable prognostic signs, whereas small, dark, and hemorrhagic blisters indicate a less favorable prognosis.

Table 1. "Poor" or Good Frostbite Prognosis Adapted from Gonzaga et al[14]

Poor Prognosis Signs	Good Prognosis Signs
Cool skin after rewarming	Warm skin after rewarming
Digit numbness	Intact sensation
No pain with rewarming	Pain with rewarming
Dusky or blue digits	Pink digits
Hemorrhagic bullae	Clear bullae

A two-tier classification that can be alternatively used in the field following rewarming. If "poor" prognosis signs (left column) are identified, patients are at increased risk of having severe frostbite sequelae. If "good" prognosis signs (right column) are identified, patients are at a lower risk of developing severe frostbite sequelae. In both cases, care or further work up should not be delayed.

Classification of Frostbite

Historically, frostbite has been divided into four "degrees" based on depth of injury similar to burns. In recent years, many centers have adopted the Cauchy et al frostbite graded classification, which is based on the presence of lesions after rewarming and radioactive uptake on bone scans. (**See Supplemental Digital Content 1,** which summarizes frostbite grade. **http://links.lww.com/PRSGO/C222**.) This classification system is advantageous because it provides an early prediction of bone and tissue loss and a likely anatomic amputation level.[9,13]

In the field, these "four-tier" classifications can be difficult to assign, as frozen tissue obscures physical examination findings. Frostbite lesions evolve slowly and may also change in appearance after rewarming, making the depth of tissue damage unclear for several days to weeks.[9] Alternatively, in the field, after rewarming but prior to imaging, patients can be categorized by a two-tier classification. This requires assessing the affected tissue for signs and symptoms of vascular compromise, providing an initial evaluation of "good" versus "poor" prognosis (Table 1).[9,14,15]

Field Management

If patients are suspected to have a cold-related injury, primary survey should be conducted according to traditional ABCDE (airway, breathing, circulation, disability, exposure) sequence, and primary first aid and resuscitation should be administered accordingly. Once frostbite has been identified, action should be made to mitigate further damage by avoiding cold exposure and removing tight, wet clothing. Rubbing, massaging, and applying dry heat to frostbitten skin should be avoided, as this can lead to additional skin and soft tissue injury.[9] The frostbitten area can be gently wrapped with dry gauze and immobilized to protect against further mechanical damage. If the affected tissue spontaneously rewarms, the patient should remain in a warm area to prevent refreezing, as this can cause additional reperfusion injury.[16,17] Once stabilized, patients should be transported to the nearest medical facility.

Rapid Rewarming

The mainstay of frostbite management is rapid rewarming in water (40–42°C) until the affected skin appears red/purple, typically taking approximately 15 minutes to 1 hour. The affected area can have impaired sensation; therefore if a thermometer is unavailable, an unaffected limb can be placed into water to prevent burn injury.[8,9] As rewarming is initiated, it is essential to circulate the water to avoid fluctuating temperatures and water cooling, which may exacerbate tissue damage. If a whirlpool is unavailable, a circulating bath can be created by placing a bucket in a sink with running water while monitoring temperature. The addition of an antiseptic solution (eg, povidone-iodine or chlorhexidine) to the rewarming bath should also be considered, as it carries the potential benefit of reducing bacterial load on the skin and is unlikely to be harmful.[9] Intense pain during rewarming may ensue; therefore ibuprofen is recommended (12 mg/kg divided twice daily with a maximum dose of 2400 mg/day) for both its analgesic properties and antiinflammatory effects of reducing prostaglandins and thromboxanes, which are associated with thrombosis and ischemia.[2,9]

Acute Hospital Management

In the hospital setting, intravenous (IV) access should be obtained. Rehydration can be performed with oral fluids, if the patient can tolerate, or small IV boluses of warm normal saline as slow infusion may lead to the cooling of IV fluids.[9] The current literature does not recommend prophylactic systemic antibiotics, which should be reserved for cases where there is significant trauma, other infectious sources, or concern for cellulitis or sepsis.[8,9]

Following rewarming, blisters may form. Providers can selectively drain clear or cloudy blisters via needle aspiration, as they may contain prostaglandins and thromboxanes that can damage the underlying tissue. Hemorrhagic blisters signify deeper tissue damage and should be left intact[9,18] After potential blisters are treated, topical aloe vera can be used to decrease prostaglandin and thromboxane synthesis, which has been shown to improve tissue

Table 2. Summary of Field and Acute Hospital Management in Frostbite Injury. Initial Frostbite Management Requires Protecting the Affected Area from Mechanical Trauma and Refreezing, followed by Rewarming

Initial Frostbite Management
1. Remove wet clothes and jewelry
2. Protect from mechanical trauma and immobilize affected tissue by loosely wrapping in dry gauze
3. Protect affected area from refreezing
4. Rapid rewarming in 40–42°C circulating water until tissue becomes red (15 min–1 h)
5. Administer Ibuprofen (12 mg/kg divided twice daily with a maximum dose of 2400 mg/d)
6. Fluid resuscitation (IV or PO)
7. Selectively drain clear blisters; hemorrhagic blisters should be left intact
8. Apply aloe vera if available
9. Loosely wrap affected tissue in dry gauze
10. Administer tPA if there are no contraindications and significant perfusion deficits are identified on bone scan or angiography

Pain management, fluid resuscitation, and lesion protection are also necessary in initial frostbite management.

survival.[9,19,20] Affected tissue should be loosely wrapped with dry sterile dressings, and cotton balls should be placed between affected fingers/toes to provide protection and decrease friction. Tetanus vaccine should be administered per standard guidelines.[9] Table 2 summarizes the initial management of frostbite injury.

Radiography

A major challenge in the management of frostbite is determining the extent of injury to appropriately preserve as much viable tissue as possible. To combat this challenge, a wide array of imaging techniques, including plain radiography (X-ray), laser and ultrasound Doppler, angiography, multiphase bone scintigraphy (bone scans), and single-photon emission computed tomography fused with conventional computed tomography (SPECT/CT), have been used to precisely define the severity, depth, and extent of injury.[14,21,22] (**See figure, Supplemental Digital Content 2,** which summarizes radiographic imaging techniques used in frostbite management. **http://links.lww.com/PRSGO/C223**.)

Since frostbite injury may occur concurrently with trauma, a post-rewarming X-ray is useful to assess for fractured bones, penetrating trauma, or foreign bodies.[2,13] In instances where signs and symptoms of vascular compromise is suspected, Doppler imaging and angiography can be used to assess vessel patency. Initially, Doppler imaging may be more favorable, as it is less invasive, but if severe frostbite is suspected, angiography should be performed as it is more specific in assessing the exact level of vessel compromise. Several studies have demonstrated improved digital salvage rates in patients when vessel compromise is identified by digital subtraction angiography and subsequently treated with thrombolytics within 48 hours of injury.[21,14,22] While protocols for thrombolytics vary between institutions, if thrombolytics are administered, angiography should be repeated every 12–24 hours to monitor treatment response.[23,24] However, angiography should be selectively used in patients prone to or with a history of renal disease given the need for contrast dye load.

Bone scans using technetium 99m-labeled diphosphonate and single-photon emission computed tomography fused with conventional computed tomography (SPECT/CT) can be used to assess depth of injury, tissue viability, and further evaluate the need for thrombolytics. Bone scans provide valuable information on blood flow, soft tissue, and bone perfusion based on the three-timing phases of radioactive uptake. Findings from bone scans can then be utilized to guide surgical management and give early predictions of amputation prognosis. Most protocols recommend bone scans for patients with second- to fourth-degree frostbite between 2–4 days postinjury and repeated 7—8 days post-injury. Absence of tracer uptake on day 7 or 8 suggests amputation will likely occur. Table 3, modified from Millet et al, describes the three timing phases for bone scans, and how they can be used to determine physiological significance and treatment options for frostbite injury.

SPECT/CT fuses radiographic uptake patterns with conventional CT to provide both anatomic and functional information on the same image. According to Kraft et al, SPECT/CT is superior to bone scan alone, because this hybrid system provides increased anatomic precision and identifies areas of decreased signal uptake that is essential for surgical planning.[14,22,25]

Thrombolytic Therapy

Thrombolytic administration, specifically tissue plasminogen activator (tPA), has demonstrated promise for use in frostbite management and has been shown to

Table 3. Bone Scan Significance for Frostbite Care

Tracer Phase				
Vascular Phase Time: Simultaneously with Injection	**Soft Tissue Phase Time: 3–10 min after Injection**	**Bone Phase Time: 2–4 h after Injection**	**Physiologic Significance**	**Treatment**
Normal	Normal	Normal	Tissue is completely viable	• Supportive care • Wound care
Increased	Increased	Normal to mildly increased	Reversible soft-tissue ischemia Bone is viable	• Supportive care • Wound care
Absent or diminished	Absent or diminished	Normal to mildly decreased	Day 2–3 post injury: deep soft tissue ischemia Day 7–8 post injury: deep soft tissue infarction	• Supportive care • Possible delayed tissue • Surgical debridement 2–4 wk post injury
Absent	Absent	Absent	Deep soft tissue infarction Bone infarction	• Aggressive early • Surgical debridement • If located on area that will have devastating effects on patients ADL surgical salvage should be performed with revascularized tissue prior to formation of dry eschar; 10–14 d • Amputation

Bone scans provide information based on the three tracer phase times (first three columns). The physiologic significance of each phase provides evidence-based guidance for frostbite treatment and care. Adapted from Millet et al.[13]

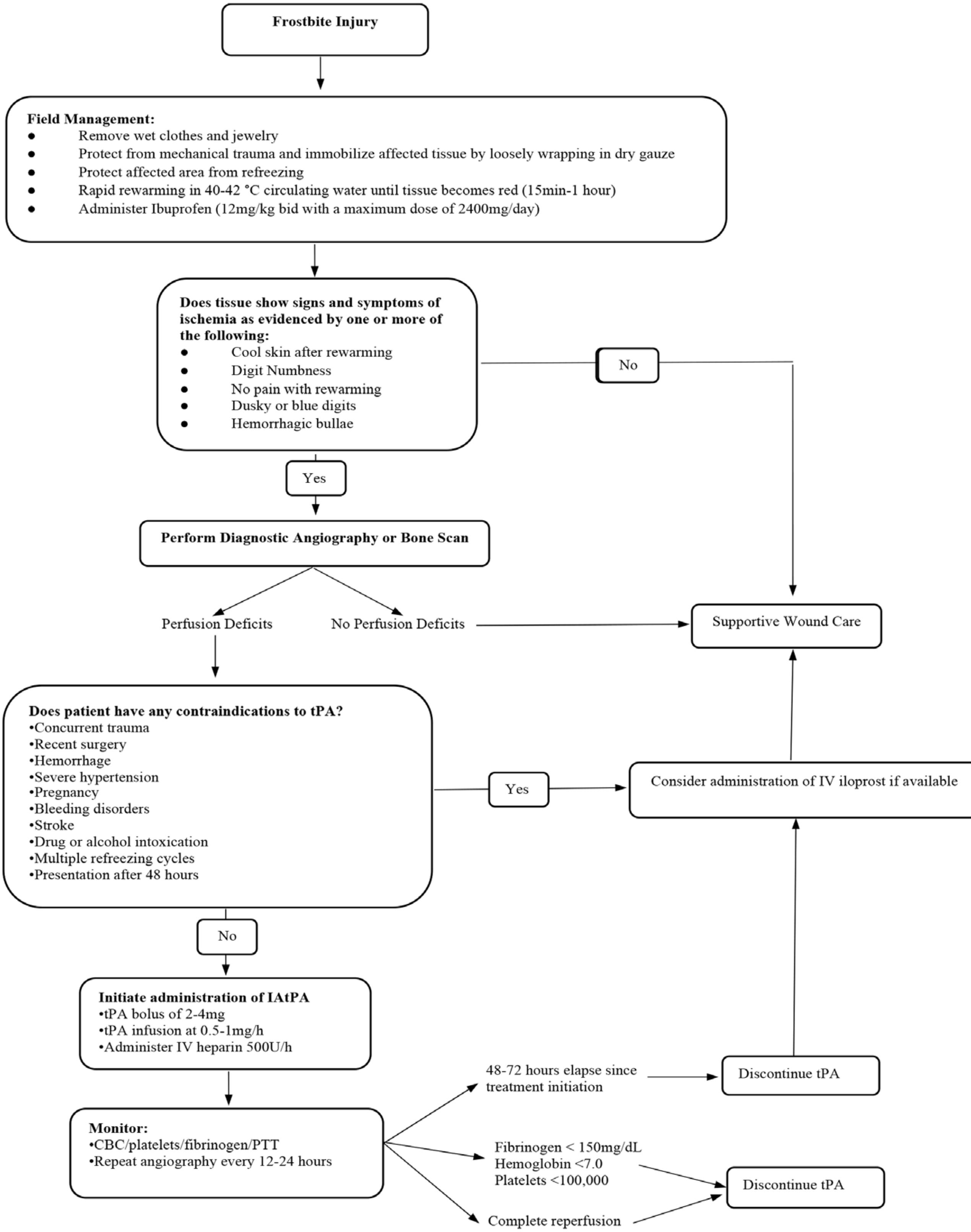

Fig. 3. Frostbite management algorithm. Key management of frostbite injury begins with proper field management, and rapid rewarming. Following rewarming, identification of tissue ischemia with diagnostic angiography or bone scans is often necessary. If tPA is administered, patients require monitoring of CBC/platelets/fibrinogen and PTT to avoid hemorrhagic events. *Abbreviations:* CBC, complete blood count; PTT, partial thromboplasmin time.

improve tissue perfusion and decrease amputations ($P < 0.05$[23]).[26–31] It can be administered either intravenously (IVtPA) or intra-arterially (IAtPA). An open label study by Twomey et al noted no difference in amputation rates between administration of IVtPA compared with IAtPA; however, IAtPA was associated with more bleeding complications.[28] Thrombolytic therapy dosing protocols vary based on IAtPA versus IVtPA administration.[32,33] During tPA administration, serial angiography should be performed every 12–24 hours to ascertain improvement in perfusion and discontinued if no improvement is noted after 48–72 hours. IV heparin should be co-administered with IAtPA to prevent the propagation of thrombosis. At the conclusion of tPA therapy, patients should be transitioned to therapeutic dosing of low molecular weight heparin for 7 days along with 325 mg of aspirin for 1–3 months.[8,23,26,24] A proposed protocol for IAtPA and its contraindications is depicted in Figure 3.

If IAtPA is contraindicated, or there is partial or no response to IAtPA, IV iloprost, a synthetic prostacyclin analog, can be used as a completion therapeutic option as it has been demonstrated to reduce digit amputation.[27,30] In a randomized controlled trial, Cauchy and colleagues showed that patients treated with iloprost had 0% amputation rates in comparison with those treated with buflomedil or IV iloprost and IVtPA, with amputations rates of 39.9% and 3.1%, respectively.[30] IV iloprost is not available in the United States; however, it may be an useful adjunct in countries where it is available.[6,30]

Surgical Management

Grade 1 frostbite should heal without the need for surgery. However, frostbite grade 2–4 often require surgical procedures.[7] Surgical intervention for frostbite injury can be grouped into three categories: acute, subacute, and delayed.[34] In the acute setting, debridement is performed

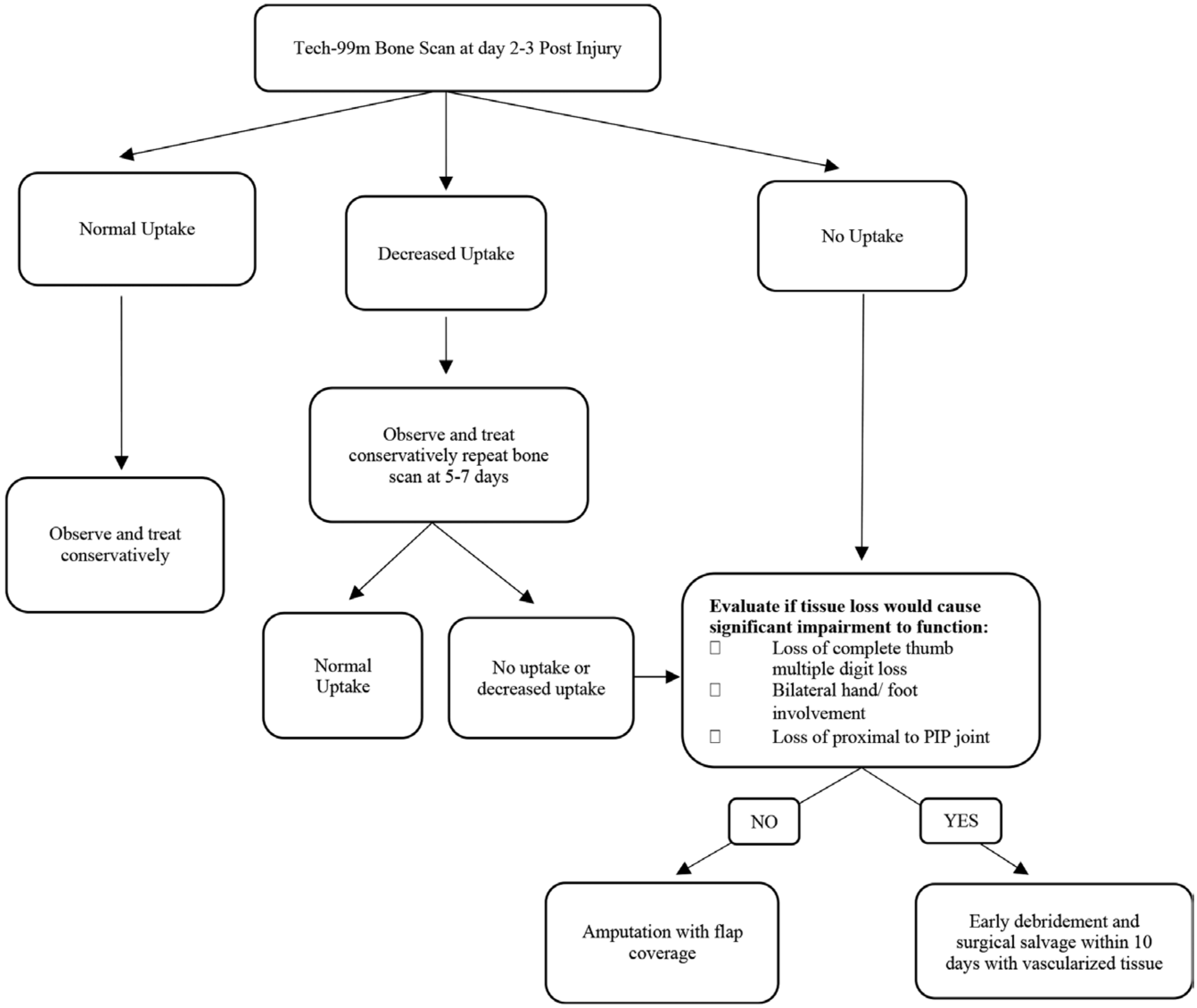

Fig. 4. Algorithm for surgical salvage adopted from Su et al. Patients with decreased or absent Tec-99m uptake on bone scans should be considered for surgical salvage by assessing affected area and quantifying tissue loss. Injuries that are prognosticated to promote significant impairment of function requires early debridement and surgical salvage within 10 days (before dry eschar forms) using vascularized tissue. *Abbreviations:* PIP, proximal interphalangeal joint.

if there are signs of infection or gangrene.[8,34] If compartment syndrome is suspected, urgent fasciotomy is indicated. Clinicians should have a high index of suspicion for patients who complain of progressive pain that is disproportionate to injury. Although compartment syndrome is rare in the acute setting, a swift diagnosis with intracompartmental catheter measurements is crucial because as compartment pressures increase, further ischemic damage to nerves and muscle will ensue.[8,35,36] Typically, compartmental pressures above 30 mmHg (normal 0–8 mmHg) necessitate emergent fasciotomy.[35]

In the subacute setting, patients who demonstrate no uptake on bone scans may undergo surgical salvage with revascularized tissue. Greenwald and colleagues demonstrated it is advantageous to revascularize and salvage structures that typically have low metabolic rate such as bone and tendon by performing early superficial surgical debridement with subsequent tissue coverage.[37,38] This should be pursued in situations where the amount of tissue loss would be detrimental to hand function, such as probable loss of total thumb, multiple digits, or extensive hand lesions.[39] Surgical salvage should be performed before the development of dry eschar (10–14 days postinjury) to provide at-risk tissue with a new blood supply to preserve both digital length and function.[34,39–41] An algorithm for evaluating patients for surgical salvage is detailed in Figure 4.

To ensure maximal tissue viability, the previous standard of care was to allow frostbitten tissue to autoamputate, which varied between 3 and 6 months.[8,34,42] Today, bone scans and SPECT/CT can measure the extent of damage within the first week of injury.[25,34,43] Therefore, the current literature recommends delayed surgery (2—4 weeks after injury) with soft tissue debridement and bone scan-guided amputations.[37,39,40] To restore previous form and function after delayed surgery, dermal tissue grafts, local flaps and free flaps can be utilized.[34,38,41,44] Importantly, selection considerations for optimal flaps include matching skin color, thickness, durability, sensibility as well as matching tissue bulk and recipient vessel size.[36,45,46]

Hand Frostbite Reconstruction

Frostbite of the hand often requires complex reconstruction toward preserving digital length and restoring form and function.[22,34,46] Patient satisfaction should be considered to ensure they can maximize their specific activities of daily living (ADL) and avoid cosmetically unappealing digits.[6,36] Surgical reconstruction may require grafts, local or free flaps, and finger transpositions to decrease pain, degree of digital tissue loss, and frostbite morbidity, all while maintaining dexterity.[2,22,34,39,46–48] As each finger has important functions for ADL, maximal preservation of digital length is key, especially in the thumb.[36,41,47] (**See figure, Supplemental Digital Content 3,**[49,50] which displays the location and reconstruction options for upper and lower extremity. **http://links.lww.com/PRSGO/C224**.)

Foot Frostbite Reconstruction

The foot is the most common location of frostbite injury. Surgical reconstruction of the foot is often necessary in frostbite injury toward restoring patients to optimal form and function.[44] Reconstruction of the foot poses several challenges because the plantar skin is adapted to contain unique thick tissue and glabrous skin necessary to resist the forces associated with weight bearing and bipedal movement. This unique microanatomy combined with the lack of a robust blood supply limits the arch of rotation and adherence of local grafts and flaps.[44,51] Therefore, surgical reconstruction of the foot requires special consideration with flaps that have sufficient skin composition, turgor, and padding while maintaining flexibility and support for walking.[38,51] Possible reconstruction options for foot defects are shown in **Supplemental Digital Content 3** (**http://links.lww.com/PRSGO/C224**).

Complications

Patients with frostbite injury often suffer from long-term complications. A scoping review with five different studies reported that 341 of 493 patients (67%) had long-term complications from frostbite injury, including neuropathy, chronic pain, cold hypersensitivity, hyperhidrosis and functional impairment.[10] Management of these long-term complications are challenging; therefore, early use of chronic pain specialists and medications such as amitriptyline, gabapentin, duloxetine, and topical capsaicin are beneficial.[6,7] Additionally, surgical and chemical sympathectomies as well as Botox injections have been proven to decrease pain and Raynaud-associated symptoms.[8,10,52]

DISCUSSION

Technological advancements have made it possible for people to travel and live in colder environments, making frostbite more common in the civilian population. However, there is no standardized reporting system for frostbite; therefore, its true incidence and prevalence as well as diagnosis and management options remain unknown.[53] This paucity of information may also be contributing to the lack of a consensus opinion on frostbite management strategies as well as high rates of complications.[6,12] Current treatment protocols vary from mitigating progressive ischemia with thrombolytics to reconstruction using flap and graft-based approaches. However, a practical guide for time-sensitive surgical approaches and the precise role of plastic surgery in frostbite care has yet to be outlined.

Timing of surgical interventions in frostbite care is controversial, in part, due to its delayed clinical manifestations. In contrast to burns, ischemic damage occurs over days and damage may not be visible until 24–48 hours when damage is irreversible. Previous dogma was to "freeze in January, amputate in July." Recently, the standard has shifted to early surgical management ascertained through radiographic imaging. Imaging also allows for the administration of limb salvaging medication such as tPA, which optimizes future reconstructive options in the plastic surgeon's armamentarium. Reconstructive strategies must be tailored to each patient's situation, depending on the location of frostbite lesions and timing of presentation. Further, because most frostbite injuries occur in areas without a robust blood supply, these procedures often require expertise in vascular anatomy as well as extensive knowledge of the reconstructive ladder.[54]

Therefore, current evidence suggests that early plastic surgery involvement may fill current gaps in frostbite management toward decreasing morbidity.

CONCLUSIONS

This review provides a comprehensive overview of frostbite management, with emphasis on the role of plastic surgery in frostbite management. While a consensus on management options for frostbite has not been fully described, published reports have demonstrated the advantages of rapid rewarming, thrombolytics, radiographic-guided surgical salvage with revascularized tissue, and various reconstructive techniques. In all management options, timing is key because the longer the tissue is ischemic the more severe the injury becomes. Frostbite complications can be devastating for many patients, and management requires a multidisciplinary team that understands frostbite sequalae to avoid delay in treatment. Specifically, as discussed herein, plastic and reconstructive surgeons play an essential role and must be well versed in frostbite management towards improving patient satisfaction and outcomes.

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REFERENCES

1. Heil K, Thomas R, Robertson G, et al. Freezing and non-freezing cold weather injuries: a systematic review. *Br Med Bull.* 2016;117:79–93.
2. Murphy JV, Banwell PE, Roberts AH, et al. Frostbite: pathogenesis and treatment. *J Trauma.* 2000;48:171–178.
3. Carceller A, Javierre C, Ríos M, et al. Amputation risk factors in severely frostbitten patients. *Int J Environ Res Public Health.* 2019;16:E1351.
4. Nguyen TQ, Song DH. Pathophysiologic difference between frostbite and burn injury and implications for therapy. *J Surg Res.* 2012;174:247–249.
5. Schellenberg M, Cheng V, Inaba K, et al. Frostbite injuries: independent predictors of outcomes. *Turk J Surg.* 2020;36:218–223.
6. Lindford A, Valtonen J, Hult M, et al. The evolution of the Helsinki frostbite management protocol. *Burns.* 2017;43:1455–1463.
7. Hutchison RL. Frostbite of the hand. *J Hand Surg Am.* 2014;39:1863–1868.
8. Handford C, Thomas O, Imray CHE. Frostbite. *Emerg Med Clin North Am.* 2017;35:281–299.
9. McIntosh SE, Freer L, Grissom CK, et al. Wilderness medical society clinical practice guidelines for the prevention and treatment of frostbite: 2019 Update. *Wilderness Environ Med.* 2019;30(4S):S19–S32.
10. Regli IB, Strapazzon G, Falla M, et al. Long-term sequelae of frostbite—a scoping review. *Int J Environ Res Public Health.* 2021;18:9655.
11. Biem J, Koehncke N, Classen D, et al. Out of the cold: management of hypothermia and frostbite. *CMAJ.* 2003;168:305–311.
12. Rintamäki H. Predisposing factors and prevention of frostbite. *Int J Circumpolar Health.* 2000;59:114–121.
13. Cauchy E, Chetaille E, Marchand V, et al. Retrospective study of 70 cases of severe frostbite lesions: a proposed new classification scheme. *Wilderness Environ Med.* 2001;12:248–255.
14. Millet JD, Brown RK, Levi B, et al. Frostbite: spectrum of imaging findings and guidelines for management. *Radiographics.* 2016;36:2154–2169.
15. Gonzaga T, Jenabzadeh K, Anderson CP, et al. Use of intra-arterial thrombolytic therapy for acute treatment of frostbite in 62 patients with review of thrombolytic therapy in frostbite. *J Burn Care Res.* 2016;37:e323–e334.
16. Lorentzen AK, Davis C, Penninga L. Interventions for frostbite injuries. Cochrane Injuries Group, ed. *Cochrane Database Syst Rev.* 2020;12(12):CD012980.
17. Cauchy E, Davis CB, Pasquier M, et al. A new proposal for management of severe frostbite in the austere environment. *Wilderness Environ Med.* 2016;27:92–99.
18. Heggers JP, Robson MC, Manavalen K, et al. Experimental and clinical observations on frostbite. *Ann Emerg Med.* 1987;16:1056–1062.
19. Golant A, Nord RM, Paksima N, et al. Cold exposure injuries to the extremities. *J Am Acad Orthop Surg.* 2008;16:704–715.
20. Imray C, Grieve A, Dhillon S; Caudwell Xtreme Everest Research Group. Cold damage to the extremities: frostbite and non-freezing cold injuries. *Postgrad Med J.* 2009;85:481–488.
21. Lee J, Higgins MCSS. What interventional radiologists need to know about managing severe frostbite: a meta-analysis of thrombolytic therapy. *AJR Am J Roentgenol.* 2020;214:930–937.
22. Joshi K, Goyary D, Mazumder B, et al. Frostbite: current status and advancements in therapeutics. *J Therm Biol.* 2020;93:102716.
23. Bruen KJ, Ballard JR, Morris SE, et al. Reduction of the incidence of amputation in frostbite injury with thrombolytic therapy. *Arch Surg.* 2007;142:546–51; discussion 551.
24. Paine RE, Turner EN, Kloda D, et al. Protocoled thrombolytic therapy for frostbite improves phalangeal salvage rates. *Burns Trauma.* 2020;8:tkaa008.
25. Kraft C, Millet JD, Agarwal S, et al. SPECT/CT in the evaluation of frostbite. *J Burn Care Res.* 2017;38:e227–e234.
26. Jones LM, Coffey RA, Natwa MP, et al. The use of intravenous tPA for the treatment of severe frostbite. *Burns.* 2017;43:1088–1096.
27. Poole A, Gauthier J, MacLennan M. Management of severe frostbite with iloprost, alteplase and heparin: a Yukon case series. *CMAJ Open.* 2021;9:E585–E591.
28. Twomey JA, Peltier GL, Zera RT. An open-label study to evaluate the safety and efficacy of tissue plasminogen activator in treatment of severe frostbite. *J Trauma.* 2005;59:1350–1354; discussion 1354.
29. Ibrahim AE, Goverman J, Sarhane KA, et al. The emerging role of tissue plasminogen activator in the management of severe frostbite. *J Burn Care Res.* 2015;36:e62–e66.
30. Cauchy E, Cheguillaume B, Chetaille E. A controlled trial of a prostacyclin and rt-PA in the treatment of severe frostbite. *N Engl J Med.* 2011;364:189–190.
31. Tavri S, Ganguli S, Bryan RG Jr, et al. Catheter-directed intraarterial thrombolysis as part of a multidisciplinary management protocol of frostbite injury. *J Vasc Interv Radiol.* 2016;27:1228–1235.
32. Wagner C, Pannucci CJ. Thrombolytic therapy in the acute management of frostbite injuries. *Air Med J.* 2011;30:39–44.
33. Lacey AM, Rogers C, Endorf FW, et al. An institutional protocol for the treatment of severe frostbite injury—a 6-year retrospective analysis. *J Burn Care Res.* 2021;42:817–820.
34. Shenaq DS, Gottlieb LJ. Cold injuries. *Hand Clin.* 2017;33:257–267.
35. Brandão RA, St John JM, Langan TM, et al. Acute compartment syndrome of the foot due to frostbite: literature review and case report. *J Foot Ankle Surg.* 2018;57:382–387.
36. Mohr WJ, Jenabzadeh K, Ahrenholz DH. Cold injury. *Hand Clin.* 2009;25:481–496.

37. Leonard LG, Daane SP, Sellers DS, et al. Salvage of avascular bone from frostbite with free tissue transfer. *Ann Plast Surg.* 2001;46:431–433.
38. Classen DA. Free flap coverage of bilateral frostbite of the feet. *Plast Reconstr Surg.* 2000;106:1316–1320.
39. Su CW, Lohman R, Gottlieb LJ. Frostbite of the upper extremity. *Hand Clin.* 2000;16:235–247.
40. Greenwald D, Cooper B, Gottlieb L. An algorithm for early aggressive treatment of frostbite with limb salvage directed by triple-phase scanning. *Plast Reconstr Surg.* 1998;102:1069–1074.
41. Fisher OL, Benson RA, Venus MR, et al. Pedicled abdominal flaps for enhanced digital salvage after severe frostbite injury. *Wilderness Environ Med.* 2019;30:59–62.
42. O'Connell JJ, Petrella DA, Regan RF. Hypothermia – Frostbite. 9. Available at https://www.bhchp.org/sites/default/files/BHCHPManual/pdf_files/Part2_PDF/Hypothermia.pdf. Retrieved October 3, 2022.
43. Manganaro MS, Millet JD, Brown RK, et al. The utility of bone scintigraphy with SPECT/CT in the evaluation and management of frostbite injuries. *Br J Radiol.* 2019;92(1092):20180545.
44. Fodor M, Bota O, Fodor L. Simultaneous extended ALT flaps for foot salvage after severe frostbite. *J Burn Care Res.* 2016;37:e383–e386.
45. Woo EK, Lee JW, Hur GY, et al. Proposed treatment protocol for frostbite: a retrospective analysis of 17 cases based on a 3-year single-institution experience. *Arch Plast Surg.* 2013;40:510–516.
46. Kamei W, Yago H, Morioka K, et al. Bilateral multiple fingertip reconstruction with free medialis pedis flaps for treating frostbitten fingertips: a case report. *Int J Surg Wound Care.* 2020;1:76-83.
47. Foucher G, Nagel D. Pinch reconstruction by hand to hand finger transfer associated with hallux transfer after a severe frostbite injury. *J Hand Surg Br.* 1999;24:617–620.
48. Borovikov A. Toe-to-hand transfers in the rehabilitation of frostbite injury. *Ann Plast Surg.* 1993;31:245–250.
49. Das De S, Sebastin SJ. Soft tissue coverage of the digits and hand. *Hand Clin.* 2020;36:97–105.
50. Rehim SA, Chung KC. Local flaps of the hand. *Hand Clin.* 2014;30:137–151.
51. Simman R, Abbas FT. Foot wounds and the reconstructive ladder. *Plast Reconstr Surg Glob Open.* 2021;9:e3989.
52. Khan MI, Tariq M, Rehman A, et al. Efficacy of cervicothoracic sympathectomy versus conservative management in patients suffering from incapacitating Raynaud's syndrome after frost bite. *J Ayub Med Coll Abbottabad.* 2008;20:21–24.
53. Nygaard RM, Endorf FW. Frostbite in the United States: an examination of the national burn repository and National Trauma Data Bank. *J Burn Care Res.* 2018;39:780–785.
54. Janis JE, Kwon RK, Attinger CE. The new reconstructive ladder: modifications to the traditional model. *Plast Reconstr Surg.* 2011;127:205S–212S.