REVIEW ARTICLE

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Diagnosis and Treatment of Frostbite

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Seventy-five years ago, when the thousands of military casualties from frostbite in World War II were fresh in the public consciousness, a 1947 issue of the *Journal* contained a review of the subject and its management.[1] The authors described a remarkable, though small, series of experiments in rabbits, human volunteers (patients with endocarditis and conscientious objectors), and two patients in whom local freezing injuries had been successfully ameliorated with immediate heparinization. The authors noted clinically important variation in the effects of experimental standardized cold exposures (hindlimb immersion in cold alcohol for rabbits and timed skin contact with dry ice or cold metal for humans). Immediate heparinization did not gain general acceptance, and treatment options remained stagnant. Over time, however, interest in hematologic intervention has reemerged in light of the potential of thrombolysis to reduce tissue loss from severe frostbite in carefully selected patients.[2]

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NOMENCLATURE AND CLASSIFICATION

The term frostbite denotes tissue damage from exposure to extreme cold. The naming conventions and classification systems are somewhat confusing and range from two-level to four-level schemes that are based on early clinical examination and more sophisticated methods, which include computed tomography and nuclear scanning of bone. Various names for nonfrozen, cold-induced tissue injury are often included in classifications, such as frostnip, chilblains, and immersion foot. Although classification schemes involving imaging may predict future amputation levels more accurately, they provide less immediate, actionable information to the clinician who is trying to determine whether an individual patient is at risk for clinically important tissue loss.[3] A four-level classification scheme, which is commonly used (Table 1), can help to provide immediate guidance based on clinical examination.[4] This scheme can be simplified by combining levels 1 and 2 as superficial frostbite, with levels 3 and 4 representing deep frostbite. A four-level classification scheme developed by Cauchy and colleagues focuses on the anatomical level of cold-induced skin lesions and bone scanning on day 2 (Table 1). This scheme can better predict the final level of amputation.[5] In all classification schemes, there is substantial overlap between levels, since the injuries are not homogeneous (Fig. 1).

PATHOPHYSIOLOGY

The pathophysiology of cold injury is a combination of direct cellular damage from freezing and cellular ischemia from vasospasm and small-vessel thrombosis.[6] Direct cellular damage results from ice-crystal formation and resulting injury to the

Table 1. Four-Level Classification Schemes for Frostbite.*

Classification Scheme	Classification Level			
	First Degree	Second Degree	Third Degree	Fourth Degree
Clinical scheme				
Depth of injury	Superficial, may include nonfrozen cold injury	Within the dermis	Full-thickness skin	Tissue beneath skin, including muscle tendon and bone
Initial findings	Reduced sensation, erythema, and burning after rewarming	Clear blistering with later sloughing of necrotic skin, pain with rewarming	Blue-gray skin discoloration; blisters that are clear, hemorrhagic, or both; pain with rewarming	Blue-gray skin discoloration, no pain with rewarming
Sequelae	None	Lasting cold sensitivity may develop	Full-thickness skin wounds, damage to growth plates in children	Full-thickness skin wounds, necrosis of underlying bone and deep tissue
	Grade 1	Grade 2	Grade 3	Grade 4
Cauchy scheme				
Extent of initial lesion	No lesion	Lesion on distal phalanx	Lesion on middle and proximal phalanx	Lesion on carpal or tarsal area
Bone scanning on day 2	Scanning unnecessary	Hypofixation of radiotracer	Absence of radiotracer uptake in digit	Absence of radiotracer uptake in carpal or tarsal area
Blisters on day 2	None	Clear blisters	Hemorrhagic blisters	Hemorrhagic blisters
Prognosis on day 2	No sequelae	Tissue amputation	Bone amputation of digit	Bone amputation of limb

* The information is from Handford et al.[4] and Cauchy et al.[5]

cell membrane, combined with intracellular metabolic derangements. Ischemic cellular damage follows endothelial disruption of the microcirculation, with vasoconstriction, thrombosis, and poorly characterized inflammatory effects on reperfusion. The severity of frostbite injury is related to the degree to which frozen tissues are reperfused on thawing.

EPIDEMIOLOGY

Throughout history, frostbite has threatened persons attempting to inhabit, contest, or explore subfreezing environments. Frostbite prevention is a major component of military and wilderness planning.[7] In recent years, the majority of frostbite cases have occurred in urban settings, where social disadvantage, physical disability, homelessness, substance use disorder, and psychiatric disease are the root causes of cold exposure that threatens life and body parts.[8,9] Even in cases of frostbite in which amputations are not required, chronic pain and dysfunction can occur.[10] Frostbite-related injuries are expensive to manage both initially and over time.[11]

PREVENTION AND FIELD CARE

The Wilderness Medical Society has published a practical guideline for the prevention and initial care of frostbite.[12] The three principal components are training, equipment, and field care. Although equipment is important, perhaps most important is proper training, with a focus on early awareness. The initial stages of hypothermia (motor and cognitive impairment) are subtle and can lead to frostbite injury. These signs and symptoms are easily missed by frostbite victims and by clinicians, if they have not been trained to anticipate them. Awareness and early intervention facilitate prevention of frostbite. Patients who are rewarmed before the freezing of body parts have generally good outcomes. Frozen body parts should not be thawed if there is a risk of refreezing before arrival at a site of definitive warming, since a freezing–thawing–refreezing injury is worse than a prolonged, simple freezing injury. Several empirical agents have been proposed for use in field care (Table 2), particularly nonsteroidal antiinflammatory agents. Among these agents, perhaps the most innova-

tive is the intravenous vasodilator iloprost,[13] although at this point, potential complications, limited supporting data, and restricted availability do not support its widespread use. Ideally, immediate care in the field would enhance flow and reverse small-vessel thrombosis in patients at high risk for major tissue loss. As more quality, efficacy, and safety data emerge and drug availability expands, protocols such as the one developed by Cauchy and colleagues, which suggest timing and weight-based dosing, may be applied more widely and remotely in patients at high risk for tissue loss.[14]

IN-HOSPITAL TREATMENT

When patients with frostbite arrive at the hospital, the primary soft-tissue problem is often in evolution. Major initial objectives are to prevent ongoing injury, identify and address coexisting hypothermia and trauma, and stratify patients according to the risk of clinically meaningful and potentially reversible soft-tissue necrosis.

MANAGEMENT OF COEXISTING ISSUES

Today, the majority of frostbite cases are due to exposure to cold in the urban setting, often in conjunction with substance use, trauma, hypothermia, physical disability, and psychosocial issues. Such issues can complicate the process of obtaining consent for treatment.

INITIAL EVALUATION AND MANAGEMENT OF FROSTBITE INJURY

An important component of the initial evaluation is identifying patients who have potentially reversible, ongoing, clinically important soft-tissue necrosis that may be ameliorated with thrombolytic intervention.[15] Patients with intact distal perfusion or no distal perfusion but a long warm-ischemia time (generally considered to be 24 to 48 hours) and those who are otherwise not candidates for thrombolysis should be treated conservatively. Such treatment consists of elevation of the injured extremity, pain control, topical wound care, selective removal or decompression of blisters, avoidance of smoking and repeat cold exposure, excision of clearly necrotic tissue, wound closure by a variety of means, and rehabilitation.[16] Management of either clear or hemorrhagic blisters is slightly controversial, with program-specific variation, and there is probably no single preferred approach. Our practice has been to débride tense blisters in order to increase comfort and motion. Patients in whom capillary flow is clearly compromised or absent after soft tissues have been thawed and warmed and in whom the warm-ischemia time is not extended (generally considered to be <24 hours) may be candidates for thrombolysis.

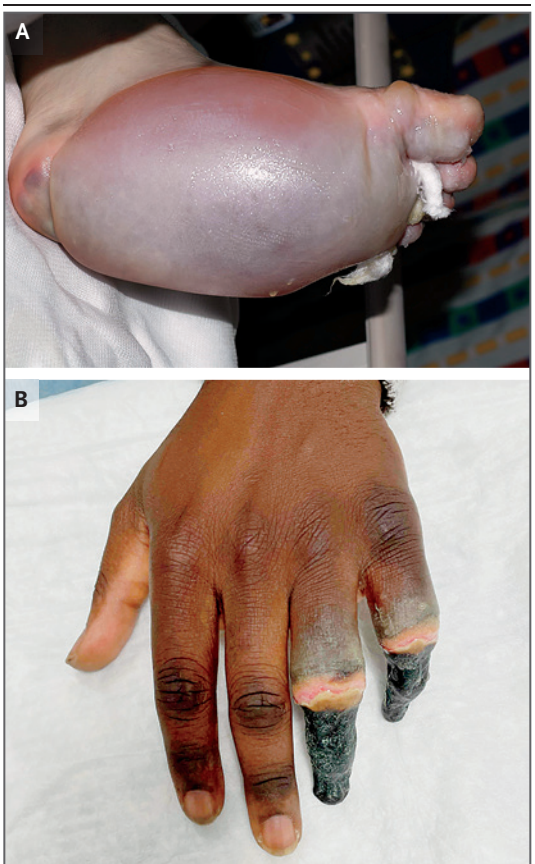

Figure 1. Clinical Images of Frostbite Injury.

Panel A shows second-degree frostbite of the foot after rewarming, with clear blisters and pink toes. Perfusion was detected in the toes. Thrombolysis was not advised, and the patient did well with conservative therapy. Frostbite can cause irreversible loss of affected tissue with marked variation in the outcome, depending on a number of factors, including the duration and intensity of cold exposure. Panel B shows the effects of prolonged exposure to freezing temperatures. The patient, a backcountry hiker (who received tissue plasminogen activator), was able to intermittently place his radial three fingers into a jacket pocket while continuing to secure equipment with his ulnar two digits, which resulted in a disparity in digital exposure.

Table 2. Potential Adjunctive Treatments in the Prehospital and Hospital Settings.

Adjunct	Supporting Evidence	Potential Benefits and Rationale	Potential Drawbacks
Hyperbaric oxygen	Case reports, anecdotes	Increased oxygen delivery to marginally perfused tissues	Risks of hyperbaric oxygen treatment (e.g., gas embolization and pneumothorax) and need for transport
Iloprost	Small, controlled trial; case reports; anecdotes	Peripheral vasodilatation may enhance peripheral perfusion, may include antiplatelet activity	Continuous infusion for 8 days, pharmacologic risks, not available in United States
Nonsteroidal antiinflammatory drugs	Anecdotes	Generic antiinflammatory and antiplatelet properties	Pharmacologic risks
Heparins	Case reports, anecdotes	Antithrombotic properties, reduced clot propagation	Pharmacologic risks
Prehospital thrombolysis	Case reports, anecdotes	Reversal of small-vessel occlusion at earlier time point	Hemorrhagic risks, possible higher systemic than angiographically directed dose of agent, potential unnecessary administration in patients without thrombosis
Antibiotics	Anecdotes	May reduce chance of wound infection	May increase antibiotic resistance without decreasing wound infection rate
Dextran	Case reports, anecdotes	May enhance small-vessel flow in injured tissue	Pharmacologic risks of agent
Tetanus toxoid, immune globulin, or both	Anecdotes	May reduce chance of tetanus infection	Pharmacologic risks of agent
Antiplatelet agents	Case reports, anecdotes	May reduce further small-vessel occlusion	Pharmacologic risks of agent
Supplemental oxygen	Anecdotes	May enhance oxygen delivery to injured tissue	Pharmacologic risks of agent
Imaging*	Case series, anecdotes	May be useful for prognostication	May not provide early actionable information in real time
Empirical fasciotomy	Case reports, anecdotes	May enhance distal flow if edema becomes a component of flow interference	Risks include anesthesia, wound infection, scar formation
Sympathetic blockade	Case reports, anecdotes	Peripheral vasodilatation may enhance peripheral perfusion	Procedural risks
Anticoagulant therapy after treatment for frostbite (with or without thrombolysis)	Case reports, anecdotes	Potential preservation of flow through damaged vessels	Pharmacologic risks

* Imaging techniques include computed tomographic angiography, positron-emission tomography, technetium-99 bone scanning, and magnetic resonance angiography.

An algorithm for the initial evaluation and management of frostbite in the hospital is presented in Figure 2. Key components are evaluation for trauma and hypothermia, evaluation for head trauma and intoxicants if mental status is depressed, a careful clinical assessment for small-vessel perfusion of involved body parts once they are thawed and warm, and estimation of the warm-ischemia time. After full rewarming, perfusion can be checked by a physical examination for capillary refill, by detection of Doppler signals in the distal pulp, and by transmission pulse oximetry of the distal digits. If small-vessel flow is absent despite full rewarming, a thoughtful risk–benefit analysis should be promptly undertaken to determine whether angiography and thrombolysis are appropriate. In an individualized risk–benefit analysis, which is the key part of the decision tree, consideration of the following is crucial: the degree of potential disability if affected body parts require eventual amputation, the risks of angiographic intervention and thrombolysis, coexisting medical conditions, and the patient's ability to under-

stand and consent to a treatment that carries a risk of hemorrhagic stroke and other major bleeding complications.

Anticoagulant therapy after treatment for frostbite (with or without thrombolysis) is controversial. Practices vary widely among programs, from several months of anticoagulant therapy, antiplatelet therapy, or both to no such treatment. Data are not adequate to support guidelines or rational decision making. The risks of postdischarge anticoagulant therapy should be considered. Our local practice has included 72 hours of postlysis heparinization if thrombolytic agents have been administered and a prophylactic dose of low-molecular-weight heparin if such agents have not been administered. Outpatient anticoagulant therapy is considered on a case-by-case basis, with an unknown risk of rethrombosis balanced against the known risks of anticoagulation.

USE OF ILOPROST

Iloprost is a synthetic prostacyclin analogue that is a potent dilator of small-vessel beds in the pulmonary and systemic circulation. The agent is also an inhibitor of platelet aggregation. Iloprost is used primarily for the treatment of pulmonary arterial hypertension and is administered through inhalation with the use of a dedicated system. An intravenous form delivered by pump infusion is available outside the United States. Since vasospasm may play a role in frostbite injury by reducing flow and facilitating the thrombotic process, early trials have evaluated iloprost for the initial treatment of frostbite in otherwise healthy patients.

Cauchy et al. reported the results of a 12-year, 3-group trial involving 47 patients with frostbite and at least one digit manifesting signs of severe frostbite.[16] The patients were initially treated with aspirin and buflomedil hydrochloride, a hemorheologic vasodilator available in Europe for treatment of claudication. Subsequently, patients were randomly assigned to one of three groups: one group continued to receive aspirin and buflomedil for 8 days, another group received iloprost in place of buflomedil for 8 days, and the third group received aspirin and iloprost for 8 days, along with 1 day of intravenous tissue plasminogen activator (t-PA). The authors concluded that the amount of tissue loss and digital amputation was lessened by the administration of 8 days of iloprost. Frostbite was staged on the basis of clinical examination and bone scanning. Neither buflomedil nor intravenous iloprost is available in the United States at present. The treatments were administered without angiography, making them potentially useful in both the prehospital and hospital settings.

USE OF THROMBOLYSIS

On the basis of small studies of frostbite in animals in the late 1980s and published experience with thrombolytic agents in patients with myocardial infarction or stroke in the 1990s, program-specific reports of t-PA for frostbite began to appear in the early 2000s. These studies used historical controls at the investigators' institutions, with amputation rates as the primary end point. Perhaps most influential were the studies from the University of Utah[17] and Regions Hospital in Minnesota.[18] Reports on subsequent studies have reinforced the clinical impression that early thrombolysis may salvage some frozen hands and feet that fail to perfuse when rewarmed, but these studies all had small samples and used historical controls, which made the quality of the data problematic. A systematic review published in 2019 described 208 reported cases in which t-PA was used to treat frostbite.[19] The authors concluded that despite the universal impression that the use of t-PA may have been helpful in reducing amputation rates or increasing tissue salvage, the quality of the evidence was low; thus, controlled trials were needed. Clinical practice guidelines published by Hickey and colleagues from the American Burn Association in 2020 advised that thrombolysis be considered for frostbitten hands with no flow distal to the proximal phalanx and that the use of local protocols that have been established as safe and effective for stroke and myocardial infarction be considered.[20] The expert group believed that both intravenous administration and directed intraarterial administration are reasonable, although data supporting equivalent efficacy are limited.[21]

The concept that directed therapy enhances local efficacy while minimizing the systemic dose, although generally accepted and seemingly logical, is also not supported by data from controlled trials. Thrombolysis cannot revitalize

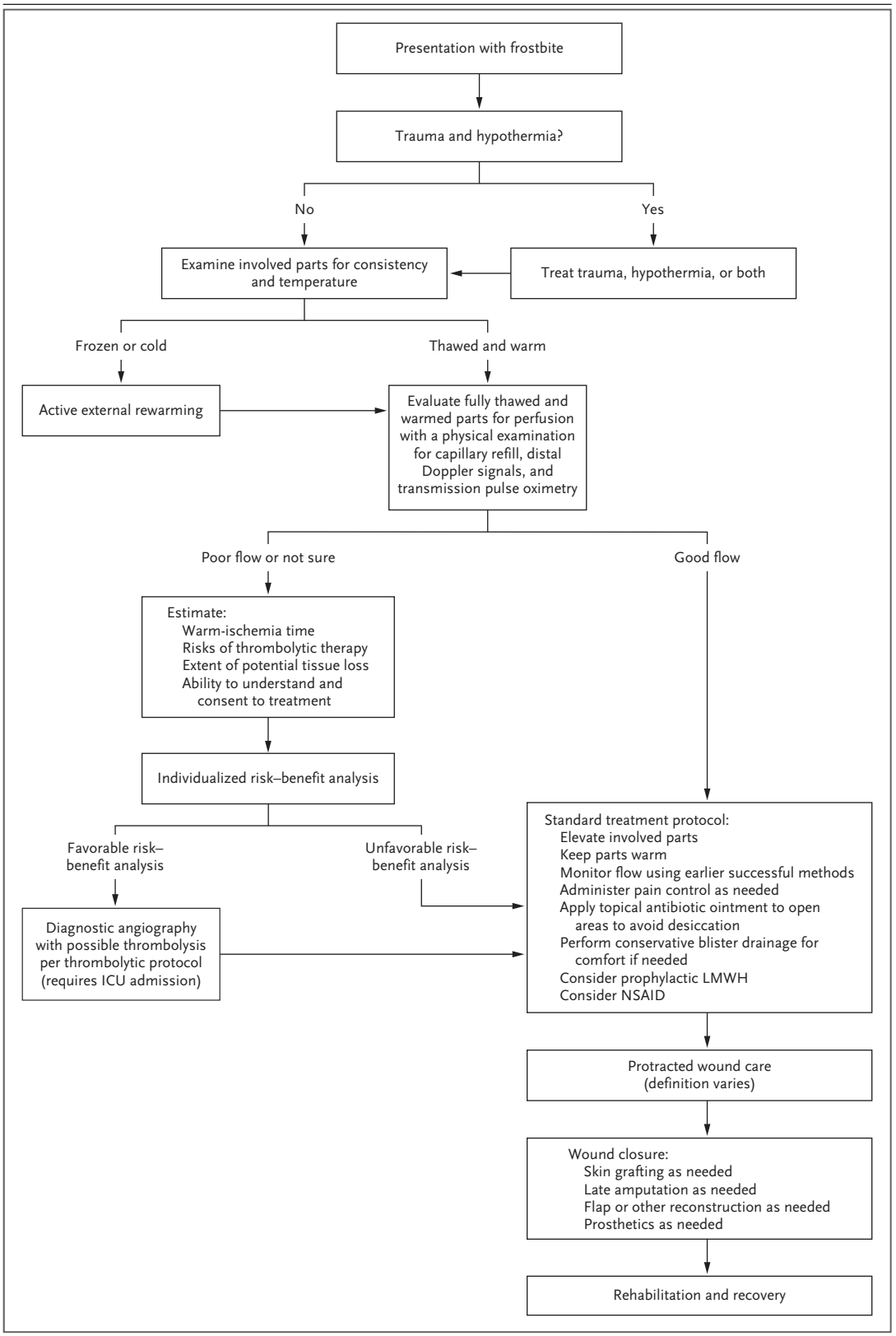

Figure 2 (facing page). Algorithm for Evaluation of Frostbite and Initial Management, with Availability of Catheter-Directed Thrombolysis.

Distal digital flow is probably adequate if Doppler signals can be heard beyond the distal interphalangeal joint or pulsatile signals can be obtained from the digital tip on pulse oximetry. ICU denotes intensive care unit, LMWH low-molecular-weight heparin, and NSAID nonsteroidal antiinflammatory drug.

tissues that are beyond salvage because of prolonged ischemia times (often difficult to clearly establish) or preexisting small-vessel disease (e.g., in patients with diabetes or prior frostbite). Thrombolysis carries clinically significant risks, including major bleeding complications and stroke. It is extremely difficult to design and complete controlled trials of treatment for frostbite, given the small numbers of patients, heterogeneity of the injuries, and short timeline for effective decision making.

CATHETER-DIRECTED THROMBOLYSIS

In facilities where rapid access to angiography is available, directed intraarterial t-PA administration is an option. Catheter-directed thrombolytic therapy with the use of angiography may be more effective per unit dose than systemic (intravenous) therapy and may help to limit doses and thereby enhance safety, but data from controlled trials that support this supposition are lacking. Through femoral arterial access (unilateral or bilateral), a 5-French catheter is used to catheterize the appropriate brachial or superficial femoral artery of the affected extremity. Digital subtraction angiography (DSA) is performed after intraarterial administration of 100 μg of nitroglycerin, which facilitates vasodilatation. Angiographic perfusion of the digits is assessed to determine whether to initiate intraarterial thrombolysis with the use of t-PA. If intraarterial thrombolysis is indicated, the catheter tip is positioned in the midbrachial artery of the most severely affected arm or the midsuperficial femoral artery of the most severely affected leg.[22] Concurrent treatment with intravenous heparin (with the goal of a partial-thromboplastin time of 40 to 60 seconds) and daily oral aspirin (81 mg) is also administered. Patients are admitted to the intensive care unit for continuous monitoring of the fibrinogen level, partial-thromboplastin time, and complete blood count during the infusion. DSA is performed the following day. On the basis of the patient's clinical status and the angiographic appearance of the affected digits, a decision is made to either discontinue thrombolysis or continue the infusion (possibly with dose adjustment) for an additional period.[23] After cessation of thrombolysis, patients receive anticoagulant therapy with heparin for 72 hours, and a course of outpatient anticoagulant therapy is considered.

OTHER POTENTIAL ADJUNCTIVE TREATMENTS

Like many disease processes without clearly effective therapies, a number of interventions have been proposed and are variably used. Some of these therapies are listed in Table 2.

SUBSEQUENT WOUND MANAGEMENT AND DEFINITIVE CLOSURE

After either conservative management or thrombolytic intervention, wound care is initially conservative because in both circumstances, the degree of ultimate deep-tissue loss is uncertain, and the goal is to maximize the length and function of an injured extremity. After a variable period, typically 1 to 4 weeks, the extent of soft-tissue necrosis is generally apparent, and necrotic tissues can be removed. Loss of the soft-tissue envelope and loss of bone are not always congruent, making each case distinct. Amputated margins typically have compromised small vessels, and a period of vacuum-assisted closure or other interventions to increase local vascularity are common before definitive closure. Wound closure proceeds with an individualized combination of skin grafts and flaps. Some authors suggest that imaging for bone and deep-tissue viability is useful for surgical planning, but this is not widely practiced.[22]

REHABILITATION AND AFTERCARE

Depending on the severity of the initial injury, rehabilitation can be daunting or trivial. Patients with cold injury may have peripheral neurologic damage that can be lifelong.[24] Many patients have persistent paresthesias and hypersensitivity, which can be triggered especially by repeat cold exposure. Permanent cold injury–induced arthritis has been reported.[25] Patients who re-

quire major amputations have a predictable set of issues shared by patients with limb loss due to other clinical problems. Neuropathic pain can be problematic,[26] and pharmacologic interventions are limited. Botulinum toxin injections have been administered empirically in highly selected patients to reduce late cold-induced vasospasm and neuropathic pain.[27] Many patients with frostbite in urban settings have preexisting issues with substance use, psychiatric problems, or post-traumatic stress disorder that need to be addressed in this phase of care.

SUMMARY

Frostbite has been a bane for soldiers and adventurers for hundreds of years. It is now increasingly common in urban areas. Thrombolytic therapy may ameliorate the terrible long-term burden of frostbite to some extent, although its use must be tempered by the possibility of serious hemorrhagic complications. Given a paucity of high-quality data, including data about thrombolytic agents, the practitioner and patient are left with difficult, time-sensitive decisions to make on the basis of the physical examination, estimated ischemia time, and risk assessment after thorough rewarming. When available, catheter-directed thrombolysis appears to have therapeutic promise in highly selected patients at risk for amputation after injury related to frostbite.

Disclosure forms provided by the authors are available with the full text of this article at NEJM.org.

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