Evaluation and Treatment in the Hospital

Overall Strategy

Frostbite is a thermal injury affecting the vasculature, microvasculature, and tissues of the extremities and as such shares many clinical features with both vascular injuries and burn wounds. This section discusses the aspects of definitive patient care, including complete patient assessment, specific evaluation of the frostbite injury regarding perfusion and tissue viability, and optimal medical management, including proper selection of candidates for endoluminal treatments such as catheter-directed thrombolysis. Early and late reconstructive surgery, ablative surgery, rehabilitation, and frostbite prevention strategies are discussed.

Initial Assessment of Frostbite and Other Injuries

A rapid and detailed clinical assessment of the patient on arrival in the emergency department is mandatory. The standard approach of assessing the airway, breathing, and circulation clearly takes precedence over assessment of the frostbite injury. History and examination may reveal coexisting problems, and although the frostbite injuries may be visually distressing and severe, it is possible that there are more serious injuries or medical conditions that need to be treated first. Particular attention needs to be paid to hypothermia, limb fractures, the peripheral circulation, and any coexisting trauma. Coexisting medical conditions such as poor glycemic control and alcohol/drug use need to be considered.

Principles

Hurley [68] stated in 1957 that frostbite will result in three zones of tissue injury: dead tissue, normal living tissue, and an interface zone. If we develop this concept further, immediately after the index frostbite injury the size of the interface zone will be maximal and is potentially salvageable. Weeks after injury, the interface zone will be negligible; as a result, the interface zone has a “dynamic” component. [47,68] The aim of early evaluation of the frostbite injury is to try to determine the exact extent of the three zones so that a subsequent multifaceted management plan may be directed to optimize tissue salvage in the dynamic interface zone.

The initial injury, individual's response, ambient temperature, and time from initial cold injury at the presentation at the hospital all contribute to how extensive the intermediate potentially salvageable interface zone will be. The patient who is transferred from the mountainside directly to the emergency department by helicopter will have a relatively large potentially salvageable interface zone when compared with a patient who has undergone a much more lengthy evacuation from a remote climbing region of the Himalayas.

Patient Care

Specialist Nursing Care

Almost all urban patients with significant frostbite should be admitted to the hospital, given that alcohol intoxication, psychiatric illness, and homelessness are common features of the urban frostbite patient; immediate discharge is rarely prudent.

Overall goals of hospital treatment include keeping the patient quiet, well nourished, suitably hydrated, and pain-free. Wound care must be meticulous to avoid further trauma. Injured extremities should be elevated above heart level to attempt to minimize edema. Physiotherapy is important, and the patient should be encouraged to mobilize as soon as possible. [192] Extremities should be treated with clean dressings and twice-daily whirlpool baths with antiseptics such as chlorhexidine or povidone-iodine. Topical Aloe vera gel should be applied every 6 to 8 hours through resolution of blisters. This encourages the eschars created by the blisters to separate from underlying healthy tissue. Although patients may be nursed anywhere that these objectives can be achieved, vascular surgery or plastic surgery/burns wards (with multidisciplinary input) tend to be most appropriate for the more severe injuries.

Frostbite blisters have been shown to contain high concentrations of the vasoconstricting metabolites of arachidonic acid, PGF$_2\alpha$ and TXB$_2$ which are known to mediate dermal ischemia in burns and pedicle flaps. It is suggested that they may play a role in the pathogenesis of frostbite, and so early debridement, either with needle aspiration or surgical debridement, is
Techniques to Evaluate Tissue Perfusion

Over the years, several diagnostic tests have been used to attempt to predict severity and prognosis of frostbite injury. These include plain radiographs, infrared thermography, angiography, triple-phase bone scanning, laser Doppler, digital plethysmography, and magnetic resonance imaging/magnetic resonance angiography (MRI/MRA). It appears that the most promising approaches are triple-phase bone scanning and MRI/MRA. Early diagnostic angiography (before tissue plasminogen activator [t-PA]) may become the most appropriate first-line investigation for the patient presenting acutely with severe frostbite injury without significant comorbidities.

Duplex Ultrasonography

Duplex ultrasonography uses B-mode, pulsed wave Doppler ultrasonography to visualize the blood flow within a vessel and color flow Doppler imaging to visualize the structure and hemodynamics within a vessel. In a modern vascular unit, there is a move toward using duplex ultrasound examination as the first-line investigative examination, reserving angiograms for situations in which a therapeutic intervention is required. Ease of access, portability, and the ability to make repeat examinations give the technique certain advantages over other imaging modalities. Many remote research stations and even large expeditions may have portable ultrasound machines. Duplex imaging has been used in the field at altitudes as high as 7950 m (26,083 feet) (Figure 8-17, online). Ultrasound has been used to determine the need for sympathetic blockade after frostbite.

Magnetic Resonance Angiography

MRI/MRA investigation has a theoretical advantage over 99mTc bone scanning because it allows direct visualization of vessels (both patent and occluded), as well as imaging of surrounding tissues. It has been suggested that it shows a more clear-cut line of demarcation of ischemic tissue. The other advantage of MRA over angiography is that it is noninvasive. However, there are relatively few accounts of its use in frostbite evaluation in the literature.

Technetium-99m Scanning

The first description of 99mTc scanning for assessment of bone viability in patients with frostbite injuries was in 1976. The degree of accretion of the 99mTc was found to depend on integrity of the vascular supply. It was successfully used to distinguish viable from nonviable bone. However, Miller and Chasmar found that very early 99mTc bone scanning in frostbitten patients was not as accurate an indicator of the ultimate extent of tissue loss as was scanning at 5 days after injury. They also noted that lesions appeared to fluctuate in extent over a 3-week period.
Cauchy and colleagues [25,26] recognized that existing frostbite classifications were based on retrospective diagnoses and were not useful for predicting the extent of final tissue loss and prognosis for frostbite patients. The 3- to 6-week waiting period often necessary to determine severity of the lesion and resultant need for amputation often caused considerable distress for patients. They suggested a new classification system that begins at day 0 (just after rewarming) and is based mainly on the topography of the lesion and on early bone scan results. This appears to be a very useful classification for the physician and patient, in that it allows accurate determination at a very early stage of the likely extent of subsequent tissue loss (see Tables 8-1 to 8-3).

An interesting insight into some of the possible mechanisms involved in certain frostbite injuries was described by Salimi and co-workers, [156] who designed an experimental model to study the pathogenesis and treatment of frostbite. Using 99m Tc radionuclide imaging, they monitored the evolution and extent of tissue damage relative to temperature, rate of freezing, and controlled rewarming. Characteristic serial changes were demonstrated on sequential scans. Initial nonperfusion was followed by perfusion and finally again by nonperfusion; this occurred in all areas in which necrosis subsequently developed. The reappearance of nonperfusion corresponded to vascular injury. Vessel thrombosis was found on pathology examination and may be related to reperfusion injury.

These clinically relevant observations gave evidence to support the concept of temporal “perfusion flux” in blood flow to a frostbitten extremity. The initial reduction is often followed by a temporary hyperperfusion phase before the final infarction phase (probably secondary to endothelial dysfunction and thrombin accumulation). Consequently, measurement of tissue perfusion at a single time point may not be as accurate in predicting outcome as originally believed.

Additional supporting evidence for perfusion flux in frostbite comes from Cauchy and associates, [25,27] who performed a more detailed analysis of two-phase 99m Tc bone scans. Sensitivity of the technique was enhanced by performing a second scan more than 5 days after rewarming. Comparative analysis of the two scans demonstrated that some of the lesions continued to evolve between day 2 and day 8. Based on this finding, they suggested that the outcome of lesions could still be modified during this period. However, in the case of severe sepsis, the results of the first bone scan can be used as an indication for emergency amputation. [26]

Although the large retrospective study of Cauchy and colleagues using two-phase bone scintigraphy suggested that nonuptake (or low uptake) in frostbite lesions had a strong correlation with the subsequent need for amputation, another prospective study has questioned some aspects of the technique. [10] This study compared 22 controls with 20 patients with frostbite. Serial scintigraphy using 99m Tc was performed in some patients. In line with the perfusion flux concept, the study suggests that scintigraphy results are somewhat more variable than previously suggested and that moderate to severe frostbite lesions can be classified as having infarcted, ischemic, or hibernating (viable) tissue, similar to the classification employed when using myocardial scintigraphy. Absence of uptake of 99m Tc, even after the initial 10 days in this study, did not necessarily indicate infarction and the need for amputation, because many such lesions retain potential for vasodilation and recovery.

Triple-phase bone scanning (using 99m Tc) has now become more widely used in specialty units, often within the first few days of presentation. This technique assesses tissue viability in an effort to allow early debridement of soft tissue and early coverage of ischemic bony structures. [58]

There are few prospective data on the efficacy of 99m Tc scanning in predicting the outcome of frostbite injuries. However, it remains a very useful way of assessing potential tissue loss [69] (Figures 8-18 to 8-21).
FIGURE 8-18 Frostbitten left hand of a climber (A) taken 36 hours after injury, while climbing in Antarctica (B) Note the discoloration and blister formation, iodine warming towels, and aseptic techniques used in tented field hospital. The digital image was reviewed within 6 hours by Christopher H.E. Inray, MD, in the United Kingdom, and management advice was given over the Internet. (Courtesy Christopher H.E. Inray, MD. From Inray C, Grieve A, Dhillon S, et al: Cold damage to the extremities: Frostbite and non-freezing cold injuries, Postgrad Med J 85:481, 2009.)
FIGURE 8-19 Condition of hands of patient in Figure 8-18 on patient's arrival in the United Kingdom, 5 days after initial injury. (Courtesy Christopher H.E. Imray, MD. From Imray C, Grieve A, Dhillon S, et al: Cold damage to the extremities: Frostbite and non-freezing cold injuries, Postgrad Med J 85:481, 2009.)
Technetium-99m bone scans performed on arrival of patient in Figures 8-18 and 8-19 in the United Kingdom. The scans show minimal perfusion to the terminal phalanges in the left hand, suggesting that amputation of the distal phalanges is likely to be necessary. (Courtesy Christopher H.E. Imray, MD. From Imray C, Grieve A, Dhillon S, et al: Cold damage to the extremities: Frostbite and non-freezing cold injuries, Postgrad Med J 85:481, 2009.)


Medical Management
Drugs used in the management of frostbite are summarized in Table 8-4.

**TABLE 8-4 -- Frostbite Management: Drugs, Doses, and Modes of Action and Rationale**

<table>
<thead>
<tr>
<th>Intervention</th>
<th>Dose</th>
<th>Action</th>
</tr>
</thead>
<tbody>
<tr>
<td>Aspirin</td>
<td>75-250 mg orally once daily</td>
<td>Antiplatelet agent, improve rheology</td>
</tr>
<tr>
<td>Ibuprofen</td>
<td>400 mg bid or tid orally</td>
<td>Antiprostaglandin effect</td>
</tr>
<tr>
<td><em>Aloe vera</em> gel or cream</td>
<td>With dressing changes every 6 hr</td>
<td>Topical antiprostaglandin effect</td>
</tr>
<tr>
<td>Oxygen</td>
<td>2 L/min above 4000 m (13,123 ft) or when <em>SpO₂</em> is below 90%</td>
<td>Improve tissue oxygenation</td>
</tr>
<tr>
<td>Hyperbaric oxygen therapy</td>
<td>2-2.5 atm 1-2 hr daily</td>
<td>Improve tissue oxygenation, improve rheology</td>
</tr>
<tr>
<td>Iloprost</td>
<td>2-10 mg/hr IV titrated against side effects</td>
<td>Vasodilator, improve rheology</td>
</tr>
<tr>
<td>Nitroglycerin</td>
<td>100 mcg IA single dose</td>
<td>Vasodilator</td>
</tr>
<tr>
<td>Papaverine</td>
<td>300 mg over 1hr IA</td>
<td>Vasodilator</td>
</tr>
<tr>
<td>Reserpine</td>
<td>0.1 to 0.25 mg once daily</td>
<td>Vasodilator</td>
</tr>
<tr>
<td>Buflomedil</td>
<td>400 mg IV or 300 mg bid orally</td>
<td>Vasodilator, improve rheology</td>
</tr>
<tr>
<td>Pentoxifylline</td>
<td>400 mg tid orally for 2-6 weeks</td>
<td>Vasodilator, improve rheology</td>
</tr>
<tr>
<td>10% Dextran 40</td>
<td>20 mL bolus, 20 mL/hr IV</td>
<td>Improve rheology</td>
</tr>
<tr>
<td>t-PA</td>
<td>1 mg/hr IA or IV</td>
<td>Thrombolytic agent</td>
</tr>
<tr>
<td>LMW heparin</td>
<td>Prophylactic dosage subcutaneously</td>
<td>DVT prevention, anticoagulant</td>
</tr>
<tr>
<td></td>
<td>Therapeutic dosage subcutaneously</td>
<td>Maintain patency of recently thrombolysed vessels</td>
</tr>
</tbody>
</table>

* This table is intended to be used as a potential frostbite formulary reference, not as a protocol for treatment. See text for further discussion.

Tetanus Prophylaxis

Frostbite should be considered to be a high-risk injury. Tetanus prophylaxis status should be completed in all patients according to currently accepted guidelines.[32]

Heparin

Heparin is a naturally occurring anticoagulant that prevents formation of clots and extension of existing clots within blood vessels. Although true thrombi are not present in dilated, erythrocyte-filled vessels immediately after thawing, they form over the next few days. Heparin has been suggested as a possible treatment for frostbite.[163] Lange and Loewe[92] demonstrated its usefulness in experimental frostbite. Subsequent investigations have been unable to substantiate these findings, and there is no evidence that heparin alters the natural history of frostbite.[16] However, most experts would agree that deep vein thrombosis (DVT) prophylaxis is indicated in any relatively immobile frostbite patient.
Indications and Recommendations for Antibiotics

There has long been awareness of the potential for infectious complications in frostbite patients. The metabolic requirements of infected and healing tissue are increased over those of normal tissue. Consequently, should the marginally perfused interface zone become infected, the resulting tissue loss is likely to be increased. Although there is little published evidence with regard to the use of antibiotics in the frostbite patient, antibiotics are widely used.

When the skin is edematous, penicillin is administered prophylactically because edema inhibits the skin's inherent streptococcal properties. If there are clinical signs of infection, antibiotic use is absolutely indicated.

Wound cultures should be taken from infected tissue to guide therapy, but while awaiting identification of species and sensitivities, practitioners should be aware that the common causative organisms include Staphylococcus aureus, β-hemolytic streptococci, gram-negative rods, and anaerobes. Empiric use of antibiotics to cover these likely organisms should be considered pending culture results.

In a 12-year retrospective study, factors found to correlate significantly with amputation were duration of exposure, lack of proper attire, remote geographic location, presence of wound infection, and delay in seeking treatment. Prophylactic systemic antibiotics did not decrease the incidence of wound infection. This paper supports the approach of deferring the use of antibiotics until a clinically relevant infection develops.

Topical: Aloe vera

Experimental evidence from the frostbite rabbit ear model has suggested a clearly defined role for thromboxane as a mediator of progressive dermal ischemia in frostbite injuries. Rapid rewarming helps to preserve tissue by limiting the amount of direct cellular injury. Selective management of blisters helps protect the subdermal plexus, and application of Aloe vera cream (e.g., Dermaide Aloe cream or gel) combats the local vasoconstrictive effects of thromboxane (Figure 8-22).

Animal studies suggest thromboxane appears to be a mediator of progressive dermal ischemia in frostbite. In a rabbit ear frostbite model, Heggers and associates compared the effect of (1) the antiprostanoïds (methylprednisolone), (2) aspirin combined with Aloe vera, (3) methimazole, and (4) a control group that received no therapy. Methimazole treatment gave 34.3% tissue survival; Aloe vera, 28.2% survival; aspirin, 22.5% survival; and methylprednisolone, 17.5% survival. In a human study of 154 patients with frostbite, there was significant improvement in outcome and reduction in amputation rates of treated patients compared with controls (p < 0.001). It was concluded that morbidity of progressive dermal ischemia in frostbite may be decreased by therapeutic use of inhibitors of the arachidonic acid cascade.

Antiprostaglandin Agents

Nonsteroidal antiinflammatory drugs, such as ibuprofen, act as a necessary adjuvant to rewarming, because they inhibit inflammatory reactions and pain by decreasing prostaglandin synthesis. Oral administration of ibuprofen decreases
systemic levels of thromboxane. Ibuprofen 400 mg may be given by mouth and should be continued at a dose of 12 mg/kg of body weight per day.

McCauley and co-workers [111] treated 38 patients with frostbite in a protocol designed to decrease production of thromboxane locally and prostaglandins systemically. All patients recovered without significant tissue loss. Increased tissue survival was demonstrated experimentally with preservation of the dermal microcirculation by using antiprostaglandin agents and thromboxane inhibitors.

**Vasodilators**

The equation determining fluid flow within a tube was first described by the French physician and physiologist Jean Poiseuille in the 1840s. He demonstrated that flow was related to perfusion pressure, radius, [41] length, and viscosity. In a frostbite patient, each of these parameters (other than length) can be optimized using appropriate medical interventions.

Iloprost

Prostaglandin E$_1$ (PGE$_1$) is a vasoactive drug that dilates arterioles and venules, reduces capillary permeability, suppresses platelet aggregation, and activates fibrinolysis. Its intra-arterial use has been effective in treating ischemic peripheral vascular disease.

The potentially beneficial effect in treating frostbite injuries with intra-arterial PGE$_1$ was first assessed in an animal model. [195] PGE$_1$ reduced the magnitude of frostbite injury when the injured limb was slowly rewarmed. The data suggested a possible role for the use of PGE$_1$ in frostbite patients who have not undergone rapid rewarming. Since the first description of its use in patients, [59] PGE$_1$ has been used with some success in frostbite injuries. [69,192]

Further experimental evidence implicates an inflammatory process in the underlying mechanism of tissue injury. It has been postulated that progressive ischemic necrosis is secondary to excessive TXA$_2$ production, which upsets the normal balance between prostacyclin (prostaglandin I$_2$) and TXA$_2$. [132]

A recent study [241] printed as a research letter showed a promising decrease in the digit amputation rate with the use of intravenous iloprost in severe frostbite injuries. The clinicians compared results of a trial of 47 frostbite patients who were rapidly rewarmed, received 250 mg of aspirin and 400 mg IV buflomedil, and who were then randomized to receive 250 mg aspirin per day, plus either buflomedil, iloprost, or r-TPA with iloprost. The iloprost group had the lowest overall amputation rate, and though the ideal dose is undetermined, this encouraging data will most likely lead to more clinical research and hope for future frostbite victims.

Iloprost is best given as an IV infusion either through a peripheral or central line in a specialist vascular or high-dependency unit. The diluted iloprost should be delivered by an accurate rate delivery system such as a syringe driver. The infusion is started at a rate 2 mg/hr and incrementally increased up to 10 mg/hr; titrated against the side effects of facial flushing, headache, nausea, and flulike symptoms; and infusion is usually run for 5 days. [69,70]

Reserpine

Reserpine is a powerful vasodilator that acts by inhibiting uptake of norepinephrine into storage vesicles. [137] For frostbite, it is used intra-arterially. The first description in the treatment of frostbite was by Snider and colleagues. [169] An animal study suggested that a regional “medical sympathectomy” may be beneficial in reducing tissue loss following frostbite, especially when rapid rewarming cannot be performed. [168]

Pentoxifylline

Pentoxifylline, a methylxanthine-derived phosphodiesterase inhibitor, has been widely used to treat intermittent claudication, arterial disease, and peripheral vascular disease and has yielded some promising results in human frostbite trials. [62] It increases blood flow to the affected extremity, increases red cell deformability, decreases platelet hyperactivity, helps normalize the prostacyclin–to–TXA$_2$ ratio, and has been shown to enhance tissue survival. Pentoxifylline is also presumed to lower pathologically increased levels of fibrinogen and so may protect against vascular endothelial damage. The drug’s efficacy has been demonstrated in animal studies and approaches the effectiveness of Aloe vera. The combination of pentoxifylline and Aloe vera appears to be synergistic. [116] A similar synergy of aspirin and pentoxifylline was demonstrated in an animal study. [143] Hayes and co-workers [62] have proposed a treatment using pentoxifylline in conjunction with the traditional therapy of rewarming, soaks, pain management, and vesicle debridement. They recommend 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.

Buflomedil

Buflomedil hydrochloride is a vasoactive drug that may have a number of effects, including inhibition of α-receptors, inhibition of platelet aggregation, improved erythrocyte deformability, nonspecific and weak calcium antagonistic effects, and oxygen-sparing activity. [28,105,108] A case series of 20 patients reported that early administration of IV buflomedil appeared to reduce the risk for subsequent amputation. [45] However, buflomedil has not been shown to reduce microcirculatory damage from acute experimentally induced freeze injury. [37] Although buflomedil does not have U.S. Food and Drug Administration (FDA) approval, it has been used extensively in France to treat frostbite, with considerable beneficial effect. [26]

Blood Viscosity

Low-Molecular-Weight Dextran

It has been observed that shortly after thawing, cold-injured vessels become dilated and filled with clumps of erythrocytes. These clumps can be easily dislodged by gentle manipulation and do not represent true thrombosis. Although the mechanism that leads to erythrocyte clumping is not completely understood, it may reflect cold-induced increase in blood viscosity. This suggests that use of low-molecular-weight (LMW) dextran may be beneficial for early treatment of frostbite. Although no controlled clinical trial of LMW dextran has been reported, there has been experimental evidence to support its use. Weatherly-White and colleagues [190] demonstrated that use of LMW dextran, 1g/kg/day, protected against tissue loss in the rabbit ear model. This led to the suggestion that the use of 1 L of 6% dextran IV on the day of injury, followed by 500 mL on each of 5 successive days, might be of benefit. [151] The extent of tissue necrosis was also found to be significantly less than in controls when hemodilution with dextran was combined with water bath rewarming with our present understanding of the etiology of frostbite and introduction of newer techniques such as t-PA, there appear to be fewer instances when LMW dextran may be used and have a demonstrable benefit.

Endovascular Interventions

Thrombolysis With Tissue Plasminogen Activator

Treatment of embolic and thrombotic peripheral vascular disease has changed radically over the last 10 years. In 1963, Fogarty and co-workers [43] reported treating acute occlusion of a peripheral vessel by a remote embolectomy catheter technique. The artery is surgically opened distant to the site of the embolus. A deflated catheter balloon is passed from the proximal artery beyond the embolus, the balloon is then inflated, and the catheter withdrawn, removing the embolus. More recently, catheter-directed thrombolysis has been used to clear distal arteries and the microvasculature using a thrombolytic agent such as t-PA. Found in vascular endothelial cells, t-PA has fibrinolytic action and plays an important role in the dynamic balance between clot formation and lysis. Plasminogen and t-PA bind to the fibrin surface of the thrombus, resulting in production of plasmin and subsequent dissolution of the thrombus. t-PA has been used extensively in coronary, cerebrovascular, and peripheral arterial disease. [131]

A small retrospective study reported successful use of catheter-directed intra-arterial t-PA to reduce amputation rates in frostbite. [17] Among the six patients who received t-PA within 24 hours of injury, 6 of 59 (10%) affected fingers or toes were amputated, compared with 97 of 234 (41%) among those who did not receive t-PA. It was postulated that rapid clearance of the microvasculature improves tissue salvage. The protocol in this study employed a 2- to 4-mg bolus of t-PA after the catheter was secured and total maximum dose of 1 mg/hr run continuously while simultaneous heparin was given at 500 units/hr through the access sheath and continued for 72 to 96 hours. When there was evidence of digital flow by angiography, t-PA was discontinued. The clinicians noted that there was limited benefit for administration of t-PA when treatment was started more than 24 hours after the initial injury.

Twomey and associates [176] reported another series using 0.15 mg/kg IV t-PA bolus, followed by 0.15 mg/kg/hr infusion over the next 6 hours to a total dose of 100 mg. Heparin was started after completion of the t-PA infusion, and the partial thromboplastin time was adjusted to two times that of normal control. Coumarin was initiated 3 to 5 days after t-PA and continued for 4 weeks in this study, which found decreased amputation rates similar to those in the study by Bruen and colleagues. [17]

Successful use of the combination of intra-arterial t-PA and vasodilators infused coaxially has recently been described. [36] After proper rewarming, the patient undergoes an arteriogram to assess perfusion and document vascular flow cutoff if present. Clinicians describe a response rate of approximately 80% if treatment can be started early.

Current Strategy for Imaging and Thrombolysis in the Acute Phase of Frostbite
It is important to realize that the role of thrombolytic therapy in the treatment of frostbite is evolving rapidly. The aim of t-PA treatment is to attempt to clear the microvascular thrombosis. However, there are both risks and benefits to t-PA therapy, and an appropriate balance needs to be struck. 

The Patient

T-PA should be considered for patients with a “significant” deep frostbite injury presenting to an appropriately equipped unit within 24 hours of the injury. A significant frostbite injury will vary from individual to individual, dominant versus nondominant hand, occupation, hands versus feet, and existing comorbidities. The injury will usually extend proximal to the proximal interphalangeal joints. Experienced clinicians familiar with the techniques need to evaluate each injury to determine whether intervention with t-PA is justified.

Tissue Plasminogen Activator in the Field

If a frostbite patient is being cared for in a remote area, transfer to a facility with t-PA administration and monitoring capabilities should be considered if the injury has occurred recently and the patient will arrive in the specialist unit within the first 24 hours of the injury. Use of t-PA in the field setting is currently not recommended because it may not be possible to detect and treat bleeding complications.

The Hospital Unit

The hospital unit needs intensive care monitoring capabilities and the hospital should be familiar with intra-arterial angiography and t-PA. A review of absolute and relative contraindications of t-PA should be undertaken. The Massachusetts General Hospital group has proposed a screening and treatment tool for thrombolytic management of frostbite, including a protocol [165] (Table 8-5).

<table>
<thead>
<tr>
<th>Treatment Screen (Four “Yes” Answers Required to Proceed to Angiography)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Are the patient's gas exchange and hemodynamics stable?</td>
</tr>
<tr>
<td>Is flow absent after rewarming (no capillary refill or Doppler signals)?</td>
</tr>
<tr>
<td>Was the cold-exposure time less than 24 hr?</td>
</tr>
<tr>
<td>Is the warm-ischemia time less than 24 hr?</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Treatment Protocol</th>
</tr>
</thead>
<tbody>
<tr>
<td>Perform angiography with intra-arterial vasodilators</td>
</tr>
<tr>
<td>If there is still no flow after angiography with vasodilators, infuse tissue plasminogen activator (t-PA) with systemic heparinization, with priority to the hands—other sites receive a systemic dose</td>
</tr>
<tr>
<td>Repeat angiography every 24 hr</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Indications for Stopping the Infusion of t-PA</th>
</tr>
</thead>
<tbody>
<tr>
<td>When restored flow has been confirmed by angiography or clinical examination</td>
</tr>
<tr>
<td>If a major bleeding complication occurs</td>
</tr>
<tr>
<td>After 72 hr of treatment</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Postlysis Anticoagulation</th>
</tr>
</thead>
<tbody>
<tr>
<td>One month of subcutaneous low-molecular-weight heparin at a prophylactic dose</td>
</tr>
</tbody>
</table>
Choice of Imaging in the Patient Presenting Within 24 Hours of Injury

Angiography or 99mTc scanning should be used to evaluate the initial injury and monitor progress after t-PA per local protocol and resources. Angiography is an invasive procedure but allows both diagnostic and therapeutic measures to be carried out, unlike 99mTc scanning, which is only diagnostic. Logical practice dictates that angiography be used to monitor intra-arterial t-PA and 99mTc scanning used to monitor IV administration of t-PA. There is no evidence to demonstrate superiority of one imaging modality over the other.

Choice of Imaging in the Patient Presenting After 24 Hours of Injury

In patients with delayed presentation (greater than 24 hours from the time of injury), 99mTc [25-27] or MRA [8] can be used to predict at an ultraearly stage the likely levels of tissue viability/amputation where t-PA is not being considered.

Papaverine

Papaverine is a powerful topical and intravascular vasodilator that is used clinically as a smooth muscle relaxant in microvascular surgery and has been used to treat cerebral vasospasm. [78] The exact mechanism of action remains to be determined, but it appears that inhibition of the enzyme phosphodiesterase, thus causing elevation of intracellular cyclic adenosine monophosphate levels, may be key. This might improve outcomes in early frostbite. When used in conjunction with intra-arterial t-PA in older patients, papaverine appears to cause a less pronounced drop in systemic blood pressure than does intra-arterial nitroglycerin in older adults. [35]

Adjunctive Treatments

Sympathectomy

Cutaneous vessels are controlled by sympathetic adrenergic vasoconstrictor fibers, and vascular smooth muscles have both α- and β-receptors. Because vasodilation of the extremities is passive, maximal reflex vasodilation occurs after sympathectomy.

The role of sympathectomy, either surgical (open or minimally invasive) or chemical, has yielded mixed results. Early sympathectomy, performed within the first few hours of injury, increases edema formation and leads to increased tissue destruction. However, if performed 24 to 48 hours after thawing, it is believed to hasten resolution of edema and decrease tissue loss. [173] Sympathectomy may have a role in preventing some long-term sequelae of frostbite, such as pain (often caused by vasospasm), paresthesias, and hyperhidrosis. [173]

In a study of 66 persons with frostbite, 15 patients with acute, bilaterally equal severe injuries were treated with immediate intra-arterial reserpine in one limb and ipsilateral surgical sympathectomy. Efficacy of therapy was assessed by comparison of the sympathectomized limb with the contralateral untreated limb. There was no conservation of tissue, resolution of edema, pain reduction, or improved function in sympathectomized limbs compared with those treated with intra-arterial reserpine. One patient demarcated more rapidly, and one other patient appeared to be protected from recurrent injury. Sympathectomy was not effective therapy for acute frostbite, even when achieved early with intra-arterial reserpine. Late protection against subsequent cold injury appears to be the only benefit of surgical sympathectomy for frostbite. [14]

Because surgical sympathectomy is irreversible, great caution should be exercised when considering its use, particularly with the advent of alternative IV vasodilators. Many would argue there is now no role for its use in the early management of frostbite.

Hyperbaric Oxygen

Evaluating the effectiveness of use of hyperbaric oxygen (HBO) in the management of frostbite is difficult. Several animal studies have demonstrated it to be of no benefit, [125] yet two recent studies in humans have yielded excellent results. [41,185] Although the proposed mechanisms of action are multiple, the major changes are postulated to occur in the microcirculation. HBO reportedly increases erythrocyte flexibility and decreases edema formation in postischemic tissues, and it is bacteriostatic. Such actions may counteract the vascular congestion, platelet aggregation, and infiltration of leukocytes seen in the microcirculation of frostbite patients. Finderle and Canker [41] report successful HBO treatment of a patient at 2.5 atm for 90 minutes daily for 28 sessions in a multiplace chamber, without significant tissue loss; this treatment started 12 days after injury. HBO may also act as an antioxidant. A series of case reports suggests significant beneficial effects from HBO. [5,44,127,185,187] The role of HBO in frostbite therapy warrants further investigation because it is a relatively safe and
inexpensive treatment.\[188]\n
Epidural Spinal Cord Stimulation

An anecdotal case series that described epidural spinal cord stimulation versus conventional treatment reported good therapeutic effects in four young patients with frostbite of the lower limbs. The authors state the mechanism of action is unknown but the treatment is reported to have resulted in rapid recovery, reduced pain, and more peripheral level of amputation.\[3\]