The Occasional frostbite

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INTRODUCTION

While cold weather injuries and frostbite in particular are uncommon, rural Canadian physicians are likely to occasionally be confronted with a severe frostbite injury. Previous approaches to frostbite in the Canadian North have centered on amputation, however, recent care has been influenced by efforts to modernise the treatment.

Frostbite injury occurs in two phases. The first is a freezing injury characterised by extracellular ice crystal formation leading to osmotic changes compromising cell membranes: A cascade ultimately resulting in endothelial injury and tissue freezing. The second phase may be described as a reperfusion injury with release of vasoconstricting metabolites of arachidonic acid such as thromboxanes. Ultimately, ischaemia may occur as a result of distal vascular microthrombi and vasoconstriction. Advanced therapeutics such as the vasodilator iloprost and thrombolytics such as tissue plasminogen activator (tPa) are directed primarily to this second phase. In this article, we will describe the basics of frostbite pathophysiology, grading and evidence-based treatment based on available resources.

HISTORY AND DEMOGRAPHICS

Historically, frostbite was predominantly reported among military personnel. Napoleon Bonaparte's military surgeon, Baron Domonique Larrey, first described the pathophysiology of the condition following the condition's devastating impact on their army in 1812.[1]

Two populations have seen an increasing incidence of frostbite over the past four decades: Extreme adventurers and those of low socio-economic status.[2] With increasing interest and accessibility of outdoor recreation in cold environments, those with limited experience and/or inadequate preparation are at risk for developing frostbite. The British Antarctic Survey found an incidence for cold injury of 65.6/1000/year; 95% of which was for frostbite, with recreation being a risk factor.[3] A cross-sectional questionnaire of Iranian mountaineers found a mean incidence of 366/1000 population per year.[4] In our group's own case series of patients presenting to Whitehorse General Hospital with frostbite, 45% of cases were related to extreme winter recreation. Other risk factors amongst adventurers

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are dehydration, high altitude, hypoxia and exhaustion.[5]

In marginalised populations, homelessness, drug/alcohol use disorders and mental health diagnoses are the significant risk factors for frostbite. A retrospective cohort study of Minneapolis frostbite patients between 2016 and 2017 found that of 1065 frostbite patients, 67.1% had a diagnosed alcohol/drug use disorder and 35.4% were underhoused. Both risk factors were predictive of having multiple readmissions following initial presentation. As well, 21.4% of patients had a mental health diagnosis.[6] A 12-year retrospective review of frostbite patients in Saskatchewan had similar results, with 46% of patients describing alcohol consumption, 17% with a psychiatric disorder and 4% with documented recreational drug use.[7]

PRESENTATION

Cold weather injuries have a spectrum of presentation, ranging from frostnip to frostbite. Frostnip is the earliest form of cold weather injury, described by numbness and pallor without associated tissue freezing.[8] Chilblains (pernio) are cold weather injuries that are milder than frostbite, caused by repetitive humid cold exposure at non-freezing temperatures [Figure 1]. It often presents as pruritic or painful skin changes.[9]

Frostbite itself is characterised by tissue freezing, causing vasoconstriction leading to ischemia and local tissue damage. The common presentation includes skin changes and changes in sensation, such as paraesthesia or anaesthesia, with severe pain and blister formation following rewarming of the tissue. Over 90% of frostbite occurs on the hands, feet and face. Severity of the injury appears to depend on the length of exposure, absolute temperature, wind chill, humidity, clothing quality and patient factors such as microvascular disease.[10]

GRADING

The diagnosis and determination of the extent of frostbite is often clinical. Many frostbite injuries appear similar at the time of presentation, and thus, should be classified following rewarming. Prognosticating frostbite has proven to be a challenge, as the true extent of the tissue damage may only become evident 3–6 weeks post-injury.[11]

Historically, frostbite has been classified using an analogous system to degree of burn: Frostnip, first degree, second degree, third degree or fourth degree according to the depth of the injury. While this system accurately describes the wound after rewarming, it is poor in predicting the extent of tissue damage, and thus, provides limited prognostic value.[12] Another, simpler system classifies injuries into either superficial or deep, with the intention that deep injuries are predictive of tissue loss.[12] Similar to the burn classification, this system does not reliably predict the prognosis. Cauchy *et al*. proposed a four-grade system for frostbite on the hand or foot that classifies the injury as it extends more proximally up the digit, as opposed to the depth.[11] In a retrospective analysis of 70 cases, they used bone scans and ultimate amputation levels to propose a classification scheme. While this system is not prospectively validated, it appears to correlate well with the findings on bone scan and amputation rates. It reflects the fact that as the cyanotic injury progresses proximally the risk of amputation increases. The value of this system is that it provides early prognostic data and may better indicate the risk of a functionally important amputation compared to the other scoring systems. In our experience, the Cauchy grading system is the easiest for clinicians to use to guide therapy. In the absence of advanced imaging, grading the case as the proximal extent of cyanosis or haemorrhagic blistering post-rewarming is recommended [Figures 2 and 3].

A valuable visible tool [Figure 2] for clinicians can be posted in an emergency department.[13]

In Figure 3 the thumb is clearly just grade 2, while one could see how both the index and long

Figure 1: Chilblains.

finger have cyanotic changes abutting the middle phalanx so arguably a 3. The ring finger is more convincingly a grade 3 with cyanosis and likely haemorrhagic blister into the middle phalanx. The fifth finger has unquestionably cyanosis and haemorrhagic blistering into the middle phalanx, so a solid grade 3.

Diagnostic imaging

While work continues in developing the optimal imaging modality to aid in directing frostbite treatment, there is as yet no consensus. Research protocols will ideally clarify the roles of radiography, computed tomography, magnetic resonance imaging, bone scintigraphy and fluorescent microangiography.[8,14-19] Currently, the rural practitioner is best to use the clinical grading system developed by Cauchy to direct therapy. In the rural setting, no imaging is required to evaluate and treat frostbite.

MANAGEMENT

Rapid rewarming

Optimal frostbite treatment begins with immediate management of hypothermia, followed by active rapid rewarming while avoiding freeze-thaw-refreeze cycles.[20] Active rapid rewarming, useful for partially frozen or frozen tissue, consists of water maintained at 37°C –39°C and actively circulated around the frozen tissue.[21] If an available hot water source is in the range of 36°C–40°C, this may be acceptable. Rewarming is complete when the tissue is soft and pliable to touch; the tissue may appear ecchymotic. Duration of rewarming varies based on affected tissue but takes approximately 15–30 min.[12] Rewarming is often painful and should be accompanied by individualised acute pain management, often with opioids.[10]

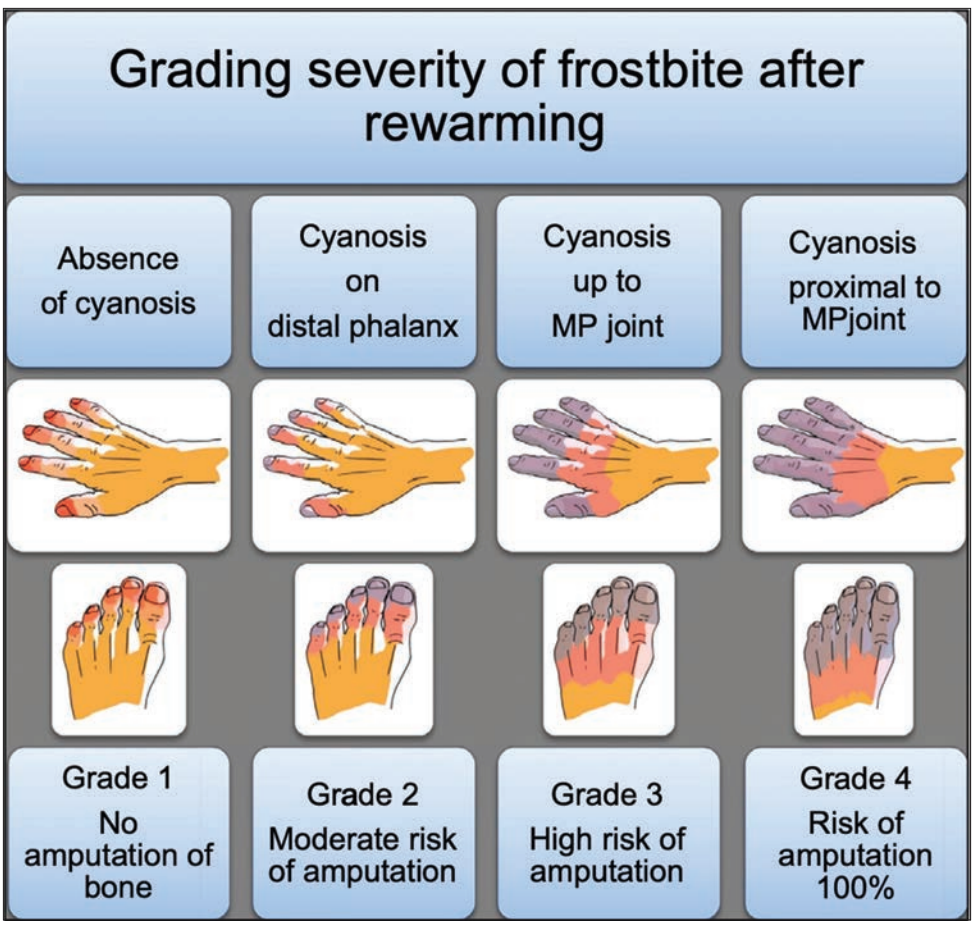

Figure 2: Grading of severity of frostbite and bone amputation risk after rewarming. Reprinted with permission from Elsevier. www.sciencedirect.com/science/journal/wilderness.

Figure 3: Grading injuries based on the most proximal level of cyanosis or haemorrhagic blistering.

Wound management

Large bullae should be drained or debrided with aseptic technique if they interfere with joint movement or if they are non-haemorrhagic.[12] Wounds should be allowed to dry appropriately. Tetanus prophylaxis is indicated as appropriate.[22] Prophylactic antibiotics are not recommended and should only be provided if there is empiric evidence of skin or soft-tissue infection. Bulky non-adherent dressings should be applied to affected areas post-management. Occlusive dressings should be avoided. Weight bearing on affected feet should be avoided. Affected limbs should be elevated to decrease inflammation and may require splinting or physiotherapy to prevent contracture formation and improve the range of motion.

Inflammation/anti-thromboxane management

The rationale for using non-steroidal anti-inflammatory drugs (NSAIDs) and aloe vera stems from early studies analysing frostbite blister fluid.[23] Thromboxane, a vasoconstricting metabolite of the arachidonic acid pathway, was found to be markedly elevated in clear frostbite blisters. A frostbite protocol was then established that used known inhibitors of thromboxane, NSAIDs and aloe vera, demonstrated by Heggers *et al*. to decrease amputation rates.[10,24,25] With no contraindications, ibuprofen can be given at 12 mg/kg/day[25] or aspirin at 325 mg PO daily.

Thrombolytic therapy

Thrombolytic therapy has extensive case series evidence suggesting a decrease in amputation rate in advanced frostbite if provided within the first 24 h.[26] Thrombolytic therapy is indicated if a patient presents within 24 h of initial insult and with severe frostbite presenting with high-risk morbidity.[14,22,27] This can range from risk for limb amputation to frostbite in digits extending into proximal interphalangeal joints. Many protocols recommend either treating clinically advanced frostbite (grade 3–4) or if there is evidence of decreased perfusion based on angiography or a technetium/bone scan.[28,29] While typically thrombolytic therapy should only be provided in a hospital setting, it has been given in austere environments.[13] Thrombolytic therapy is contraindicated if time since rewarming is >24 h, or in trauma patients. Amputation rate increases with each hour that passes (warm ischemia) after rewarming before thrombolytic agents are administered, and thus timely treatment is critical.[29] tPA is generally administered with subcutaneous enoxaparin or heparin.[27,29] A review suggested that there is no real advantage to intra-arterial administration versus intravenous.[26] If angiography or technetium scanning is available, imaging can be performed before and after starting thrombolytic therapy. tPA and heparin can also be provided intra-arterial with interventional radiology as resources allow.[30]

Iloprost

Iloprost is a prostacyclin analogue that acts as a vasodilator, inhibits platelet aggregation, and may also have profibrinolytic and cytoprotective properties. It is indicated for severe frostbite of Grade 2–4, within 72 h of initial insult.[10,22,31-33] While often used as the primary treatment, protocols have used it in cases non-responsive to thrombolysis or when thrombolysis is contraindicated.[28] Iloprost therapy does not require an available intensive care setting, but rather simply close monitoring of vital signs.[10]

Iloprost, while commonly used in Europe, is only available in Canada through Health Canada's special access program. Since its first published Canadian use in 2015, a growing number of centres across the country have gained access to it.[34] While

working in coordination with a hospital pharmacist, arranging the availability of iloprost has not proven to be an arduous endeavour for most rural hospitals in Canada. As a special-access drug, it is currently available cost free. Given its shelf life of up to 2 years, stocking a vial (one dose) or two in rural centres, and the rest in a regional centre, is reasonable. This allows for the treatment to be started as soon as possible even in more remote locals.

Two Canadian case series have demonstrated a decrease in amputation rate using iloprost as part of a comprehensive treatment protocol.[33,35] Poole *et al*. demonstrated an amputation rate for both grades 2 and 3 to be 0% while grade 4 was 50%.[33] Crooks *et al*. compared 26 patients treated with iloprost to 64 treated without iloprost over a similar period. Grade 3 patients in the iloprost group had a 18% amputation rate versus 44% in the untreated group and Grade 4 demonstrated an amputation rate in the iloprost group of 46% versus 95% in the untreated group.[35]

Continued care

The use of thrombolytic therapy and iloprost has led to promising tissue salvage. Frostbite centres can guide the acute management of frostbite in remote centres, especially if timelines for transfer may be delayed for thrombolytic or iloprost therapy. Ultimately, patients with severe frostbite require a consultation to a tertiary care or an experienced frostbite centre. This may initially be virtual. Damaged tissue may require surgical management for repeated debridement, escharotomy, fasciotomy or amputation.[36]

Sequelae

Patients who have suffered frostbite may suffer from long-term effects. In particular, cold insensitivity is common, but variable. Case reports demonstrate vasomotor disturbances, neuropathic/nociceptive pain and arthritis. There remains uncertainty as to the pathophysiology of these changes.[37] Early work using Botulinum toxin type A does show some promise in allowing a return to working in cold environments by mitigating cold intolerance.[38]

A RECOMMENDED TREATMENT APPROACH

In summary, we recommend the following treatment approach in the algorithms below [Figures 4 and 5]. If frostbite injury is suspected, then rapid rewarming is indicated. Post-rewarming, the injury should be graded using the Cauchy grading system. If the injury is Grade 1, there is no further treatment required and the patient may be discharged with advice to avoid refreezing. If the injury is Grade 2 or higher, we recommend Ibuprofen or acetylsalicylic acid (ASA) as well as topical aloe vera as an antithromboxane treatment, as shown in Table 1 for dosing. If the injury is within 72 h of rewarming and Iloprost is available, it can be given as an intravenous infusion to all Grade 2–4 injuries, [Figure 4]. If a Grade 4 injury is within 24 h of rewarming, thrombolysis through tPa may be added. If there is access to only thrombolysis and not Iloprost, we suggest using thrombolysis in grade 3 and 4 frostbite, [Figure 5]. Unlike Iloprost, it is the authors' opinion that the complication risks of thrombolysis outweigh its use in Grade 2 injuries.

The algorithms provided are an approach based on the evidence at the hand. It is acknowledged that the evidence is based on case series and requires further investigation. However, given that there are no real alternatives, many areas are proceeding with treatment *in lieu of* waiting for more definitive evidence. The algorithms are based on the Yukon protocol,[39] but differ in that Figure 5 provides guidance for those centres which do not have access to iloprost. The main decision points

Table 1: Pharmacologic dosing in frostbite

Medication	Dose
ASA	325 mg q6h PO
Ibuprofen	400 mg q6h PO
tPA (Alteplase)	0.15 mg/kg IV bolus over 15 min, followed by a continuous infusion of 0.15 mg/kg/h IV for 6 h
	Maximum dose of tPA is 100 mg/day
Enoxaparin	1 mg/kg SC BID for 12 days
	If LMWH is contraindicated, use IV heparin
	500–1000 U/h can be given for 6 h, while maintaining PTT at 2x baseline value
Iloprost	0.5 ng/kg/min IV 6 h/day for 5 days at maximum tolerable rate
	q30 min increase of 0.5 ng/kg/min to a maximum dose of 2 ng/kg/min
	Decrease rate by 0.5 ng/kg/min if the patient develops headache or hypotension

IV: Intravenous, tPA: Tissue plasminogen activator, SC BID: Subcutaneous twice a day, LMWH: Low molecular weight heparin, ASA: Acetylsalicylic acid, PO: By mouth, PTT: Partial thromboplastin time

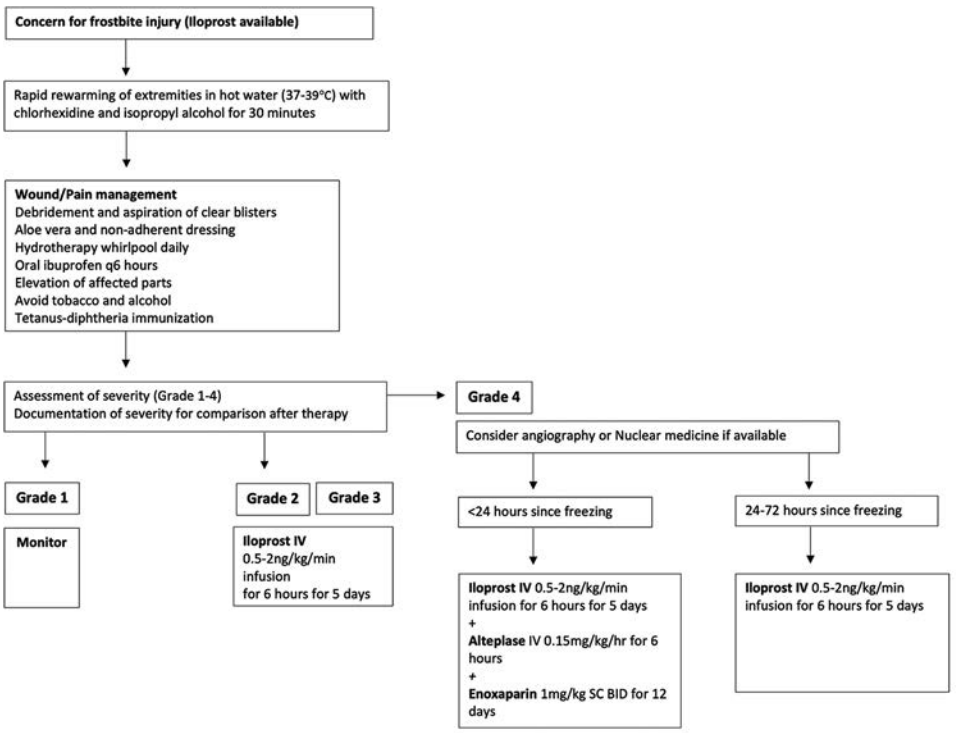

Figure 4: Frostbite treatment algorithm if Iloprost available.

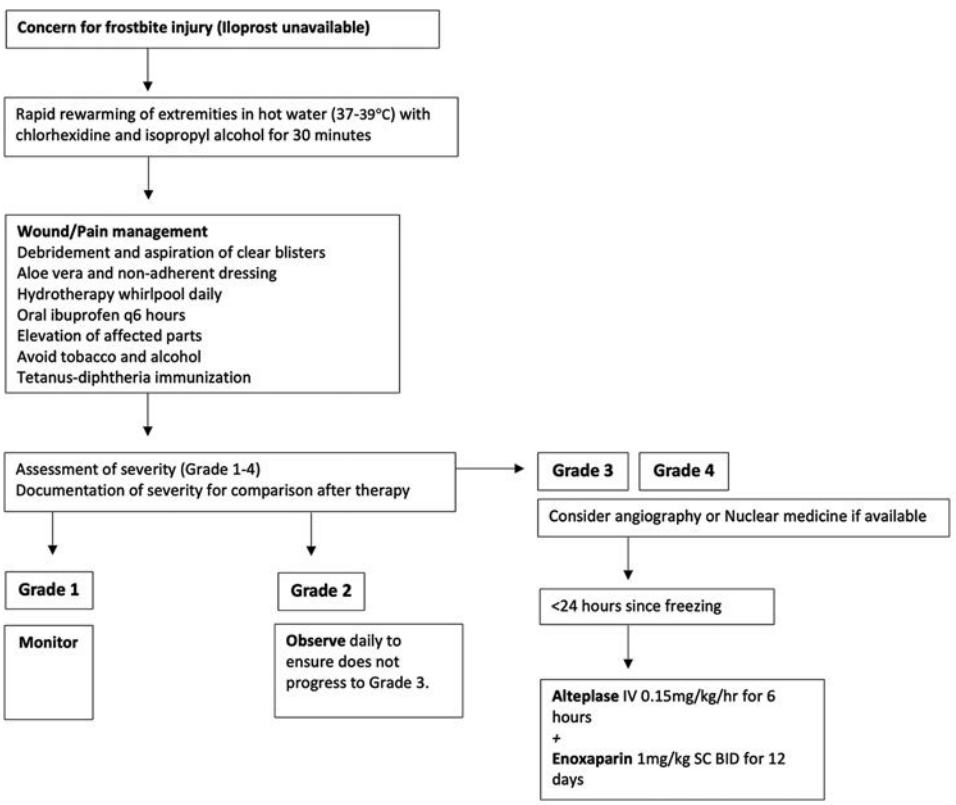

Figure 5: Frostbite treatment algorithm if Iloprost not available.

are classifying the injury as a Grades 2, 3 or 4 frostbite. If one has access to Iloprost, we suggest treating Grades 2–4 with Iloprost and only add thrombolysis in Grade 4, [Figure 4].

CONCLUSION

All Canadian rural centres will occasionally encounter frostbite. Clinicians should prioritise tissue rewarming, grading the injury to establish the prognosis and recognise that time matters for advanced cases. While based on case series evidence alone iloprost ± thrombolysitcs should be considered in severe cases, given the lack of therapeutic alternatives.

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