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CLINICAL REVIEW

Managing frostbite

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Frostbite is defined as the damage sustained by tissues while subject to temperatures below their freezing point (typically −0.55°C); in the broader sense it can include non-freezing cold injuries, where tissues do not freeze but are subject to a sustained and injurious cooling.[1] Cold injuries were historically associated with military work in the field, but in the past 20 years the number of civilian cases has increased.[2 3] The unusually cold winters in northern Europe in early 2010 caused many cases of frostbite in the United Kingdom, central Europe, and Scandinavia. The severity of frostbite injury is proportional to the temperature, duration of exposure, and amount and depth of frozen tissue.[3] The term frostbite covers a wide range of injuries, from minimal tissue damage to substantial tissue necrosis that can result in amputation. Recent advances in treatment mean that frontline medical staff must be able to recognise and treat frostbite effectively.

What factors predispose to frostbite?

Factors that predispose to freezing and non-freezing cold injury include military activities, winter sports, and homelessness (box 1).[4] In a large retrospective epidemiological review of frostbite injuries sustained over 12 years in the Canadian prairies, individual behaviour was an important contributor to overall risk. Forty six per cent of patients were intoxicated with alcohol, 17% had a psychiatric disorder, and 3% had used illicit drugs.[5] Fingers, toes, noses, cheeks, ears, and male genitalia were most commonly affected by frostbite in all groups (in that order).[6] A large cross sectional study over 19 years by the US army found that men of Afro-Caribbean descent were four times more likely than white men to sustain cold weather injuries.[7]

What pathological mechanisms are involved in the injury?

Although the precise mechanism of injury is not fully understood, the most recent laboratory research (principally using an animal model) describes a series of progressive, overlapping changes. These may be divided into "pre-freeze phase," "freeze-thaw phase," "vascular stasis phase," and "late ischaemic phase."[2] Cellular injury and ischaemia result from direct and indirect effects of a freezing insult (see figure on bmj.com).

Box 1 | Predisposing factors

General: Unusually cold weather, prolonged exposure to cold, inadequate clothing, inadequate use of appropriate clothing, homelessness, smoking, dehydration, old age, ethnic origin, high altitude
Systemic disease: Peripheral vascular disease, diabetes, Raynaud's disease, sepsis, previous cold injury
Psychiatric illness
Drugs: β blockers, sedatives, and neuroleptics
Trauma: Any immobilising injury, but especially head and spinal injuries and proximal limb trauma that compromises the distal circulation
Intoxication: Alcohol and illicit drug use

Cellular injury

Direct tissue injury occurs through the formation of intracellular and extracellular ice crystals. Except in cases of very rapid freezing, ice crystals form in the extracellular space, increasing extracellular oncotic pressure. Cells then dehydrate through outward diffusion of water, resulting in intracellular electrolyte disturbance.[8] As tissues rewarm, extracellular ice crystals melt and increasing tissue oedema is seen. Freezing also leads indirectly to the release of proinflammatory cytokines.

Ischaemia

Freezing causes localised anomalies in blood flow. After exposure to temperatures below freezing the affected extremity exhibits localised vasoconstriction, which reduces blood flow and exacerbates cooling to produce even greater vasoconstriction. Cooling of the vascular contents also causes an increase in viscosity and microvascular damage, which precipitates local transcapillary plasma loss and oedema formation. Endothelial damage encourages the

SUMMARY POINTS

Prevention, using a combination of appropriate behaviour and equipment, is key
Rewarm frostbite as soon as the risk of refreezing is minimal
Seek advice from a specialist unit if the injury is potentially severe
Consider thrombolysis (with tissue plasminogen activator) in severe injuries presenting within 24 hours of exposure
Delay surgery unless there is evidence of compartment syndrome or overwhelming sepsis
People who have sustained a cold injury are more susceptible to a future cold injury

SOURCES AND SELECTION CRITERIA

We performed a Medline and Google Scholar search with no date limitations using the terms "frostbite", "cold injury", and "freezing cold injury" to obtain references that form the basis of this article. The content of this paper was derived from a variety of sources but we included only articles that were well written, had high clinical importance, and (where relevant) were referenced from soundly conducted clinical trials.

Box 2 | Acute and emergent conditions often seen in patients with frostbite

Hypothermia

This life threatening condition is common in people with frostbite, with a reported incidence of 12% in people with a serious cold injury.[5] Hypothermia is defined as a drop in core body temperature to below 35°C. Its presentation depends on severity. Initially, the metabolic rate increases to cause tachycardia, tachypnoea, and shivering. In more advanced cases with a core temperature below 28°C, the metabolic rate drops to produce bradycardia, hypoventilation, and reduced consciousness leading to coma and death.[13 15]

Trauma

Patients with frostbite commonly have traumatic injuries—in the Canadian study, 19% of patients with frostbite had been involved in a serious traumatic incident.[5] Frostbite should therefore be suspected in trauma patients in cold environments, especially those who have been trapped in vehicles, have sustained limb injuries that may compromise distal blood supply, and those who have experienced hypovolaemic shock.

Table 1 | Early and late features of frostbite

Early features	Late features
Affected part feels cold and possibly painful	White and waxy skin with distinct demarcation from uninjured tissues
Continued freezing produces paraesthesia or numbness (or both)	Woody, insensate tissues
Areas of blanching blending into areas of apparently uninjured skin	Progression to bruising and blister formation (usually on thawing)

Table 2 | Assessment of degree of freezing cold injury[2]

	Mild frostbite injury		Severe frostbite injury	
Clinical appearance	First degree	Second degree	Third degree	Fourth degree
Depth of tissue freezing	Partial thickness skin freezing	Full thickness skin freezing	Freezing of the skin and subcutaneous tissue	Freezing of the skin, subcutaneous tissue, muscle, tendon, and bone
Colour of tissues	Erythematous or hyperaemic	Erythematous	Blue or black	Initially deep red and mottled; eventually black and mummified
Blistering or necrosis	None	Blisters containing clear fluid	Haemorrhagic blisters and some tissue necrosis	Profound necrosis
Oedema	Minor	Substantial	Substantial	Little or none

formation of microthrombi, which occlude capillaries and lead to ischaemia.

Whether microvascular clots form mostly during freezing or thawing is unclear, but the rewarming of frozen tissues results in the lysis of ice containing cells and produces a prothrombotic microenvironment. Endothelial damage stimulates degranulation of mast cells and histamine release, which exacerbates oedema formation within tissues.[2 9 10]

Vasoconstriction may be followed by vasodilatation through the so called hunting response—a normal physiological response thought to protect the extremities from freezing; this occurs at the expense of a drop in core body temperature and may be largely ineffective in locally extreme cold stress.[11] Tissue ischaemia may result in widespread and devastating tissue loss. The most severe injuries are often seen in tissues that freeze, thaw, and freeze again. These "freeze-thaw-refreeze" cycles produce progressively severe thrombosis and tissue ischaemia.[4]

How to evaluate a patient with an apparent cold injury

History

Seek a history of how and when the cold injury occurred. Pay particular attention to the likely temperature, wind chill, and duration of exposure—factors that will probably affect the severity of injury. Other necessary information (obtain from a collateral source if the patient cannot provide it) includes the patient's premorbid state, particularly history of peripheral vascular disease and smoking status.[9]

Examination

Cold injuries can present as non-freezing or freezing cold injuries and also as mixed injuries. Mixed injuries will have a dominant component (either freezing or non-freezing cold injury), however, and there will be areas of overlap between deeper, frozen injuries and lesser affected, non-frozen regions.

Freezing cold injuries vary from extremely minor cases (sometimes referred to as frostnip) to grossly frozen limbs. Table 1 lists early and late signs and symptoms. The full extent of injury is often not apparent for some days after injury and close observation is needed during this period.

In cases of true freezing cold injury, the degree of injury may be assessed by the clinical appearance of the tissues (table 2; figs 1 and 2).

History and examination must ascertain if the injury occurred within the past 24 hours and whether it is mild or severe. Mild cases can be managed locally, but a potentially severe injury merits discussion with a specialist unit and possible transfer. Similarly, if a severe case presents less than 24 hours after injury then urgent transfer to a unit with thrombolysis capabilities must be considered, if it is safe to do so.

Non-freezing cold injury more commonly affects the feet than the hands.[12] Patients usually present with prolonged local numbness, sometimes with pain or paraesthesia (or both). After rewarming, the foot rapidly becomes hyperaemic, with local oedema and persistent severe pain. Tissue loss is uncommon, and tissues do not become woody or frozen. Discoloration from vascular stasis or cyanosis is commonly confined to nail beds, and blisters are unusual; when they do occur, the exudate is usually clear and gelatinous and seldom haemorrhagic.[1] Disabling pain and neuropathy can persist and may be very difficult to treat.

How should cold injuries be managed in the prehospital phase?

Patients presenting with frostbite may have potentially life threatening conditions, such as hypothermia, or have experienced severe trauma. Prioritise such injuries over the presence of regional cold injury, and start the rewarming of hypothermic patients and stabilisation of traumatic injuries before transport to a health facility (box 2).[3 13] Isolated regional cold injuries must be rewarmed only if the risk of refreezing is small—the patient might even have to walk on a frozen limb to receive medical care in a warm environment rather than attempt rewarming in the field. Rubbing a frozen area may cause further damage and must be avoided.[14]

Internet and satellite phones

Patients and clinicians with limited experience of frostbite can now use the internet and satellite phones to access expert advice in remote or difficult situations. A virtual opinion or more specialised advice can be sought from almost anywhere in the world using a combination of digital images and telephone advice.[2]

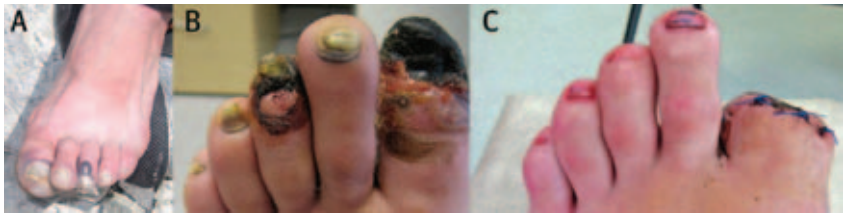

Fig 1 | A typical frostbite affecting the hallux and third left toes showing the initial injury at presentation at base camp on Everest (A), at six weeks (B), and at 10 weeks (C). Note the delayed surgical amputation of the hallux after definitive demarcation and the recovery of the third digit after appropriate management

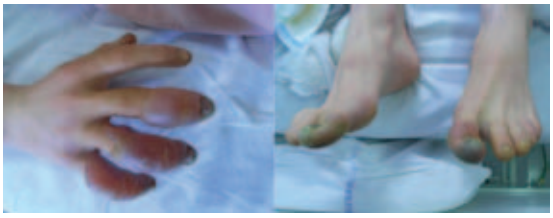

Fig 2 | Typical frostbite injuries in the hands and feet of a climber with mildly haemorrhagic bullae presenting three days after exposure. The bullae were aseptically aspirated and a five day iloprost infusion resulted in a complete recovery

How to rewarm an affected area

Once the patient is in a safe environment and freezing cold injury has been diagnosed, rapidly rewarm the affected area(s) (non-freezing cold injuries may be made more florid and have a worse outcome if they are rapidly rewarmed and should be rewarmed slowly in air at 22-27°C[16]). Warm frostbite injuries in a whirlpool bath containing a mild antiseptic such as chlorhexidine (without the affected region touching the device's hard sides) at 40-41°C for at least 30 minutes, until all tissues are thoroughly rewarmed and pliable, with a red-purple colour.[2 3 9 17] This treatment is thought to preserve the dermal circulation. Continue for 30 minutes twice daily until there is clear demarcation of necrotic tissues or evidence of tissue healing, such as epidermal regeneration and the emergence of normal skin colour. Keep the area warm and dry between treatments. This regimen has become generally accepted since a case series of 38 patients with frostbite treated this way recovered without appreciable tissue loss.[17] Foot spas are cheap and readily available alternatives. Although they cannot keep water as hot as 40°C, careful addition of warmer water and monitoring of water temperature make them useful for rewarming frozen hands or feet.

Rewarming can be acutely painful, so give all patients adequate analgesia. Ibuprofen (400 mg orally, every 12 hours) is recommended for its selective antiprostaglandin activity. Aspirin may be less beneficial in frostbite because it blocks all prostaglandins, including some prostacyclins, which may expedite wound healing.[2] Sympathectomy can be used to increase blood flow, but vasodilatory drugs such as iloprost (synthetic analogue of prostacyclin I_2) have largely superseded the need for this. Recent clinical trials have shown that the phosphodiesterase inhibitor pentoxifylline enhances tissue viability by increasing blood flow and reducing platelet activity and should therefore be considered in severe frostbite.[2]

Necrotic or potentially non-viable tissues are at increased risk of infection. Give tetanus toxoid and broad spectrum prophylactic antibiotics to patients with any risk of infection of necrotic tissue.[17] Leave simple non-tense areas of clear blistering intact because their rupture may increase the risk of infection. Tense or haemorrhagic blisters may be carefully aspirated (fig 2), but only in facilities that can maintain rigorous asepsis, because infection has been the cause of early radical amputations and death in the past.[2 3 17] Complex cases, such as patients who may have been exposed to bacteriological contamination during transit or those at risk of hospital acquired infections such as meticillin resistant *Staphylococcus aureus*, are best left with as much intact skin as possible until after discussion with a specialist unit. Areas of blistering require light bandaging with loosely applied and non-airtight dressings. Affected limbs should be raised to prevent further tissue oedema and venous stasis. Prevent patients with affected lower limbs from bearing weight as much as possible to protect fragile tissues from mechanical stress and ischaemia.

Early surgical debridement is contraindicated in almost all patients because it can take weeks for definitive demarcation of non-viable tissues to occur, and tissues that initially looked unsalvageable may recover. Exceptions to this include freeze-thaw-refreeze injuries, complicating limb trauma, infection, and compartment syndrome.[2] Even if radical debridement or amputation(s) will be necessary, it is normally best to delay surgery until at least six to eight weeks after injury because surgical trauma to proximal tissues can result in poor wound healing. Specialist advice is essential before any earlier surgery.[2 18 19]

Re-evaluation after rewarming and appropriate management often shows that surgery is not needed, despite an initial suspicion that tissues would be unsalvageable. When definitive demarcation of necrotic tissue does occur, the area may be left to auto-amputate, especially if the patient is frail or has serious comorbidities; definitive (delayed) surgical debridement should be planned in consultation with a specialist surgical unit.

Imaging

The precise severity and depth of tissue injury are usually difficult to evaluate, so early surgical debridement is contraindicated in most cases of frostbite.[3] Several investigations have been proposed for predicting the need for and extent of debridement—plain radiography, laser Doppler studies, digital plethysmography, and infrared thermography.

Box 3 | Prevention of cold injuries

Cold injuries can be prevented only by total avoidance of the cold but the following advice is useful if cold exposure is anticipated:

- Wear protective clothing (multiple loose layers provide insulation)
- Avoid tight clothing that constricts body parts, reducing blood flow
- Stay dry and avoid prolonged cold exposure
- Avoid the wind or protect against it
- Wear an insulated hat, covering the ears
- Wear gloves to protect the fingers, and in extreme cold, insulated mitts
- Wear insulated boots
- Maintain adequate nutrition and hydration
- Avoid alcohol and smoking
- Use supplemental oxygen above 7500 m
- Use chemical or electrical hand and foot warmers

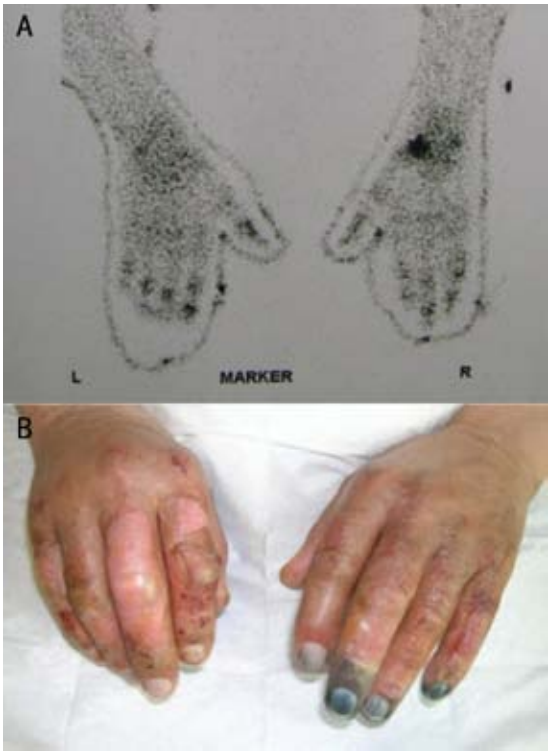

Fig 3 | (A) Technetium 99 scans of the hands of a patient with frostbite. The terminal digits have reduced signal (especially in the left hand), suggesting that substantial tissue necrosis has occurred. (B) Clinical picture after a five day iloprost infusion showing the close correlation between the initial technetium 99 scans and the subsequent clinical appearance

None of these investigations can accurately predict outcome in isolation, but they may be useful adjuncts to clinical examination in difficult or severe cases.

Technetium 99 (Tc-99) triple phase scanning (fig 3) and magnetic resonance angiography (fig 4) seem to be the most useful imaging modalities. A large retrospective review of 92 patients with severe frostbite showed that Tc-99 scans obtained during the first few days of injury accurately indicated the level (toe, hand, or arm) of amputation in 84% of cases.[20] Case reports have also shown that these scans can accurately assess injury and help determine the level of, or need for, surgical debridement.[21 22] Case reports suggest that magnetic resonance angiography is superior to Tc-99 because it allows direct visualisation of occluded vessels, effectively images surrounding tissues, and may show a clearer demarcation of ischaemic tissues, although this has not been confirmed by large scale studies.[23]

The routine use of complex imaging techniques in minor frostbite is not justified. These investigations are best reserved for severe frostbite, the few patients who might need early surgery, or those where thrombolysis is being considered; in such cases discuss the proposed management with a specialist unit first (fig 5).

Acute intravascular thrombolysis

Evidence is emerging that patients who present within 24 hours of an acute, severe frostbite injury, in whom major tissue loss is predicted should be considered for acute intra-arterial or intravenous thrombolysis.[14] This treatment aims to clear the intravascular thromboses and restore arterial perfusion of the affected limb(s), thereby partially or completely salvaging the tissue. Risks are bleeding, infection, or failure. Contraindications to thrombolysis with tissue plasminogen activator will be familiar to most doctors, but in acute frostbite the possibility of coexisting trauma must always be considered.

Patients must be managed in a high dependency ward or an intensive care setting within a major vascular unit that regularly undertakes acute peripheral thrombolysis.

A PATIENT'S PERSPECTIVE

In January 1999, I was involved in a mountaineering accident in the French Alps that tragically claimed the life of my climbing partner. After being trapped by severe weather for five days, I was rescued and taken to hospital in Chamonix. On arrival, my hands and feet were frozen, literally solid, and when thawed out it was obvious that there was much permanent damage. The doctors were hopeful that they could save parts of my hands and feet but I was warned that it would take a long time before the final outcome was known. For me this uncertainty was one of the hardest factors during what was a very troubled period. After only 10 days, though, I became increasingly unwell and developed septic shock. While I was unconscious the decision was taken to amputate.

Learning to live my life without hands or feet has been the most incredible, challenging, difficult, exciting, and rewarding experience. When I started out I was dependent on others for every daily task. Now I can walk, cook, drive, run, ski, snowboard, sail, climb mountains again, and I have a beautiful baby daughter. Life couldn't be better.

Jamie Andrew, *Edinburgh*

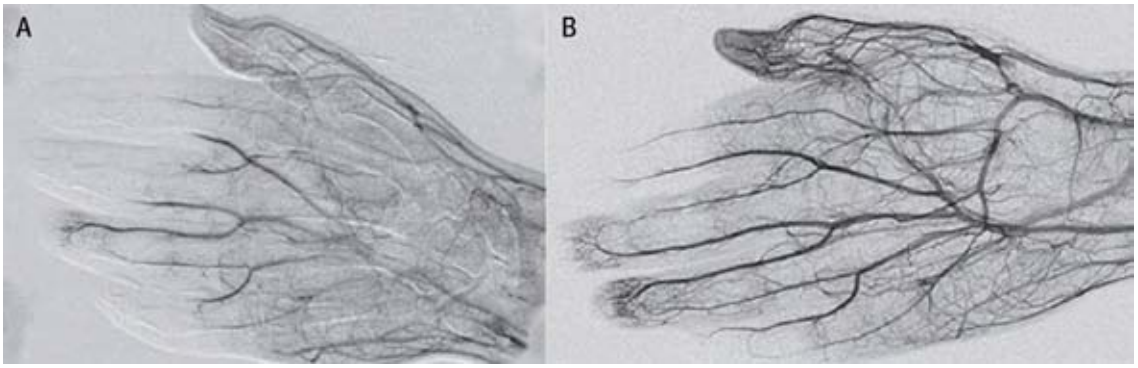

Fig 4 | Digital subtraction angiography showing the thrombotic occlusion of the terminal digits in a major frostbite injury of the hand (A) and reperfusion after urgent thrombolysis (B). Reproduced, with permission, from Sheridan and colleagues[14]

A diagnostic angiogram must be performed and an intra-arterial catheter inserted close to the site of thrombosis. Giving tissue plasminogen activator within 24 hours of injury reduced digital amputation rates from 41% to 10% (P<0.05) in one retrospective study in a single institution.[24] Reperfusion of ischaemic tissue can cause tissue oedema, and if this occurs within a confined space, interstitial pressures may rise and result in a compartment syndrome that requires urgent fasciotomy.

What other treatments might follow rewarming?

Several adjunctive treatments have been proposed but the evidence base to support their use is variable.[25 26] Topical aloe vera is widely used in North America (for its antiprostaglandin effect) in superficial frostbite. Iloprost and buflomedil are powerful vasodilators, which are used in Europe for more severe cases.[2 20] Anecdotal reports advocate hyperbaric oxygen, but no trials have been performed. Vacuum assisted closure of wounds may be useful after amputation and the technique merits study.

What are the long term sequelae of cold injury?

The most commonly encountered long term problem is that of chronic pain, probably as a result of vasomotor dysfunction. Patients have sometimes asked for otherwise healthy digits to be amputated to alleviate the pain,[9] which is often unresponsive to conventional analgesia and may be lifelong. Some (mostly anecdotal) evidence suggests that amitriptyline (usually the treatment of choice for the pain after non-freezing cold injuries) may be of benefit. Patients with refractory pain may need referral to a specialised pain service.

Many reports detail the association between the development of complex regional pain syndromes and cold sensitivity in frostbitten tissues. A study that followed 30 patients with severe frostbite injuries for 11 years showed that 53% had cold hypersensitivity, 40% had numbness of the fingers, and 33% had reduced sensitivity of touch. The authors speculate that these sequelae are secondary to thermophysiological changes in people with an increased tendency to vasospasm.[27] Thus, a single episode of frostbite can result in cold sensitisation (inability to tolerate cold temperatures in the affected area) and predispose to cold injury in the future. Cohort studies have shown that people who have had frostbite injuries have a significant lifelong risk of further injury.[28] All patients who have had frostbite therefore need preventive advice (box 3).

Other chronic morbidities

Freezing injuries may produce localised osteoporosis and in severe cases subchondral bone loss. These changes are thought to be secondary to vascular damage, so more profound bony changes may be an indicator of severity. Changes are sometimes evident a month after injury but often need longer to develop: by 16 months radiographs may show multiple lucencies in the subchondral bone.[9] In children the damage may be more serious, with undergrowth of affected bone, irregularities in the articular surfaces, and a propensity to early arthritis.[29 30]

Areas that have been frostbitten are susceptible to chronic ulceration and are prone to malignant squamous transformation, similar to Marjolin's ulcers in old burn scars.[31]

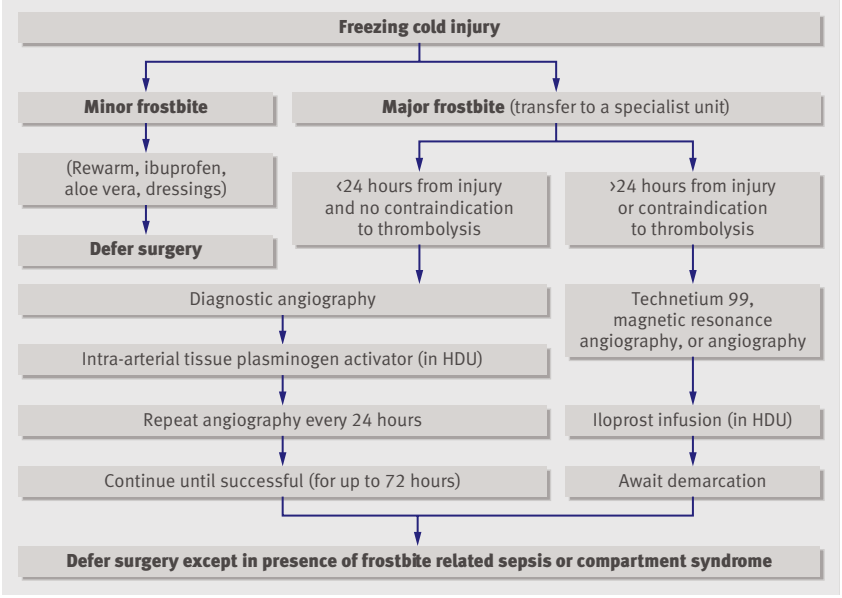

Fig 5 | Algorithm for the management of acute frostbite. HDU=high dependency unit

AREAS FOR FUTURE RESEARCH

- Formal evaluation of the use of intra-arterial tissue plasminogen activator (including the timing of treatment and the potential use of ultrasound accelerated thrombolysis)
- Formal evaluation of hyperbaric oxygen and other adjunctive treatments
- Larger long term follow-up studies to look at outcomes in patients with cold injury
- Improved prevention strategies, including developments in protective equipment; for example, recent developments in extreme altitude climbing boots are now rated down to −60°C and step-in crampons help reduce finger exposure to cold

ADDITIONAL EDUCATIONAL RESOURCES

Resources for healthcare professionals

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Imray CHE, Freer L. Frostbite. In: Auerbach PS. *Wilderness medicine*. 6th ed. Elsevier [forthcoming]

McIntosh SE, Hamonko M, Freer L, Grissom CK, Auerbach PS, Rodway GW, et al. Consensus guidelines for the prevention and treatment of frostbite. *Wilderness Med J* [forthcoming]

Resources for patients

British Mountaineering Council (www.thebmc.co.uk/Category.aspx?category=19)—Internet frostbite service run by David Hillebrandt, Paul Richards, and Chris Imray

Andrew J. *Life and limb*. Portrait Publishers. 2005

TIPS FOR NON-SPECIALISTS

- Prevention is key
- Treat any serious or life threatening conditions in the field, but do not rewarm frostbitten tissues until there is no possibility of refreezing
- Establish the likely severity of the injury and seek advice from a specialist unit for any potentially severe injury
- Rewarm mainly non-freezing cold injuries slowly, but rapidly rewarm mainly freezing cold injuries at 40-42°C for a minimum of 30 minutes in a whirlpool device or foot spa with chlorhexidine solution; continue treatment twice daily until improvement is seen
- Areas of simple blistering should be left intact, lightly dressed, and elevated; the patient must not bear weight on frostbitten tissues
- Give all patients with tissue loss broad spectrum antibiotics and a tetanus vaccination to prevent infection; consider treatment adjuncts such as thrombolysis
- Appropriate clinical management often results in the recovery of tissues that initially looked unsalvageable, so early surgical debridement is rarely beneficial
- Provide all patients with lifestyle advice, including immediate smoking cessation and the need

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Previous articles in this series

- Management of venous ulcer disease (*BMJ* 2010;341:c6045)
- Translating genomics into improved healthcare (*BMJ* 2010;341:c5945)
- Extracorporeal life support (*BMJ* 2010;341:c5317)
- Managing diabetic retinopathy (*BMJ* 2010;341:c5400)
- Investigating and managing pyrexia of unknown origin in adults (*BMJ* 2010;341:c5470)

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Patient consent obtained.

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ANSWERS TO ENDGAMES, p 1169. For long answers go to the Education channel on bmj.com

ANATOMY QUIZ

Coronal computed tomography image through the face (bone windows)

A Cribriform plate
B Inferior turbinate (concha)
C Crista galli
D Left maxillary sinus/antrum

CASE REPORT Forgotten, but not gone

1 The most likely diagnosis is congenital rubella syndrome.
2 Congenital infection can be confirmed by testing for rubella IgM or rubella IgG seroconversion, or both, in a blood sample taken from the mother during the antenatal period (or any other available stored serum) and in a serum obtained at a later date.
3 Uptake of the measles, mumps, and rubella (MMR) vaccine has fallen in recent years, allowing for circulation of rubella and measles viruses within the community.

STATISTICAL QUESTION

Reference and normal ranges

Answers *c* and *d* are true, whereas *a* and *b* are false.

ON EXAMINATION QUIZ

Congenital neck masses

Answers A, C, and E are correct, whereas answers B and D are not.

described in the published reports,[1,2] this calculation was erroneously made on the basis of the right eye only, resulting in fewer events as well as fewer people in whom a change in visual acuity could be ascertained. The published and revised numbers are presented in Table 1; the article is correct at NEJM.org. These changes do not materially change the conclusions of the study.

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A Controlled Trial of a Prostacyclin and rt-PA in the Treatment of Severe Frostbite

TO THE EDITOR: Many alternatives have been proposed for the treatment of frostbite: hemodilution, platelet-aggregation inhibitors, low-molecular-weight heparin, alpha-adrenergic vasodilators, calcium-channel inhibitors, nonsteroidal anti-inflammatory agents, prostacyclin analogues, fibrinolytic agents, and hyperbaric oxygen. None have been assessed in prospective randomized trials. Small retrospective studies[1-3] suggest the efficacy of thrombolysis or prostacyclin analogues against spasm and thrombosis.

Between 1996 and 2008, we randomly assigned 47 patients (44 men and 3 women) with severe frostbite to one of three treatment regimens in an open-label study. Severe frostbite was defined as having at least one digit (finger or toe) with frostbite stage 3 (lesion extending just past the proximal phalanx) or stage 4 (lesion extending proximal to the metacarpal or metatarsal joint).[4] The study was approved by the ethics committee at the University of Grenoble.

Directly after their mountain rescue, patients meeting the study criteria (having no contraindications to use of the study drug, no severe trauma, and no hypothermia) received care that involved rapid rewarming of the areas with frostbite plus 250 mg of aspirin and intravenous administration of 400 mg of buflomedil. They then underwent randomization to receive one of three regimens for 8 days. One group received 250 mg of aspirin and buflomedil (400 mg for 1 hour per day), the second received 250 mg of aspirin plus a prostacyclin (0.5 to 2 ng of iloprost per kilogram of body weight per minute for 6 hours per day), and the third received 250 mg of aspirin, iloprost (2 ng per kilogram per minute for 6 hours per day), and fibrinolysis (100 mg of recombinant tissue plasminogen activator [rt-PA] for the first day only). Treatment efficacy was evaluated after 8 days in all 47 study patients by means of bone scans obtained with the use of technetium scintigraphy, the results of which showed an excellent correlation with the level of final amputation required (predictive value of positive findings, 0.996).[5] (For additional details, see the table in the Supplementary Appendix, available with the full text of this letter at NEJM.org.)

In most of the patients, whose mean age was 33.1 years and who had no notable medical or surgical history, frostbite occurred at high altitude (>2000 m). Frostbite occurred in the feet in 33 patients in the hands in 29 patients, and in both hands and feet in 15 patients. The baseline characteristics of the patients and the localization of the frostbite were similar across treatment groups, except that stage 4 lesions were more common in the group receiving prostacyclin plus rt-PA.

The risk of amputation in the buflomedil group was 60% (9 of 15 patients). As compared with this group, the risk of amputation was significantly lower in the other two groups — 0% (0 of 16 patients) in the group receiving prostacyclin alone and 19% (3 of 16 patients) in the group receiving prostacyclin plus rt-PA ($P<0.001$ and $P<0.03$, respectively, by Fisher's exact test).

The efficacy of treatment with prostacyclin was confirmed when the number of digits amputated and the severity of the frostbite were considered (Table 1). However, our results do not rule out a

Table 1. Number of Amputated Digits (Fingers or Toes) According to Treatment, Severity of Frostbite, and Time to Treatment.*

Treatment Group	No. of Patients	All Stages of Frostbite		All Stages, ≤12 Hr to Treatment		All Stages, >12 Hr to Treatment		Stage 2		Stage 3		Stage 4 or Higher	
		Digits with Frostbite	Digits Amputated	Digits with Frostbite	Digits Amputated	Digits with Frostbite	Digits Amputated	Digits with Frostbite	Digits Amputated	Digits with Frostbite	Digits Amputated	Digits with Frostbite	Digits Amputated
		no.	*no. (%)*	*no.*	*no. (%)*	*no.*	*no. (%)*	*no.*	*no. (%)*	*no.*	*no. (%)*	*no.*	*no. (%)*
All groups	47	407	47 (11.5)	271	13 (4.8)	136	34 (25.0)	155	4 (2.6)	215	31 (14.4)	37	12 (32.4)
Buflomedil	15	106	42 (39.6)	48	11 (22.9)	58	31 (53.4)	31	2 (6.5)	66	31 (47.0)	9	9 (100.0)
Iloprost	16	142	0	79	0	63	0	64	0	75	0	3	0
Iloprost plus rt-PA	16	159	5 (3.1)	144	2 (1.4)	15	3 (20.0)	60	2 (3.3)	74	0	25	3 (12.0)

* Stage 2 frostbite was defined as having at least one digit (finger or toe) with frostbite, with the lesion confined to the distal phalanx; stage 3 as having at least one digit with frostbite, with the lesion extending just past the proximal phalanx; and stage 4 as having at least one digit with frostbite, with the lesion extending proximal to the metacarpal or metatarsal joint.

possible additive effect of rt-PA in selected patients. In addition, there were no significant differences according to frostbite localization, with 183 frozen fingers leading to 22 amputations (buflomedil, 49%; prostacyclin, 0%; prostacyclin plus rt-PA, 2%) and 224 frozen toes leading to 25 amputations (buflomedil, 34%; buflomedil, 0%; prostacyclin plus rt-PA, 4%). The only adverse reactions were minor (hot flushes in 55% of the patients, nausea in 25%, palpitation in 15%, and vomiting in 5%). None of these reactions led to discontinuation of the study medication.

On the basis of these results, we recommend that in the treatment of severe frostbite (stage 3 or above), after rapid rewarming, a combination of aspirin and prostacyclin should be used. The addition of rt-PA should be considered on a case-by-case basis, depending on the severity of injury (at least stage 4 frostbite), the presence of trauma (especially head trauma), any medical contraindications, and the amount of time passed since rewarming.

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CORRECTION

Effects of Medical Therapies on Retinopathy Progression in Type 2 Diabetes (July 15, 2010:363:233-44). A correction is described in the Correspondence section of this issue of the *Journal* (Update of the ACCORD Eye Study [January 13, 2011:364:188-9]).