Nonfreezing cold-induced injury (NFCI) is a clinical syndrome that results from damage caused to tissues exposed to cold temperatures at or above the freezing point of water (0 °C to 15 °C [32 °F to 59 °F]). NFCI does not involve tissue freezing, which distinguishes it both clinically and pathologically from frostbite. The earliest descriptions of this syndrome had their origins in the military. Baron Dominique Jean Larrey, Napoleon’s chief surgeon, used the word congelation to describe the nonfreezing injuries together with frostbite casualties that occurred during the 1812 assault on Russia. Historically, infantry regiments have been decimated by cold and wet conditions, and many medical advances in understanding the pathophysiology and clinical course of NFCI have occurred after wars. However, it has been observed that the continuity of research tends to lag during the periods between major military campaigns. Developments in prevention of cold injury have flourished as new clothing and footwear have been designed, but little progress has been made in the treatment of NFCI. There is a rise in the number of people pursuing recreational activities in harsh environments, and as a consequence, civilian NFCI is becoming more prevalent. However, because many physicians are unfamiliar with NFCI, it may go undiagnosed during assessment of the cold-exposed victim. This results in unnecessary hospital admissions and potentially harmful and expensive therapy. Proper education and awareness of the hazards innate to the cold environment should mean that NFCI is preventable in most circumstances. This chapter explores the history, epidemiology, pathophysiology, and current prevention and treatments of NFCI, as well as pernio (chilblains), cryoglobulinemia, and cold urticaria.
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This chapter explores the history, epidemiology, pathophysiology, and current prevention and treatments of NFCI, as well as pernio (chilblains), cryoglobulinemia, and cold urticaria.

**Epidemiology**

Individuals suffering cold and wet extremities for extended periods are at risk for NFCI. During the 1800s, NFCI was observed more frequently when the temperature hovered around the freezing point—when the ground was muddy rather than frozen. Standing or sitting for long periods, wearing constrictive footwear, malnutrition, fatigue, or the blunt trauma of marching on cold, wet feet all added to the severity of injury. Original animal studies that modeled NFCI demonstrated that cold temperatures near the freezing point were more likely to cause injury when the extremities were wet than when they were dry. Ambient temperature and wind speed can both influence cooling.

With “shelter limb” (dependency without cold) and “paddy foot” (wet but not cold), one observes an injury that has no apparent distinguishing differential feature from NFCI. This suggests that neither cold nor wet is a prerequisite to developing the injury. It appears that NFCI is a reperfusion injury that develops after a sustained period of peripheral vasoconstriction.

**MILITARY**

In combat settings, there is rarely the time, equipment, or opportunity to apply appropriate remedies to NFCI. In the 1854 Crimean War, cold injury was documented more often among the men in the trenches who were so restricted in their movements. Frequently this position happened to be the bottom of a trench knee-deep in mud and water or half-filled with snow. In November 1944, during World War II, American forces sustained 11,000 cases of trench foot. Evaluation of possible risk factors for cold injury during the 1982 war in the Falkland Islands has been published. A year after exposure, there were no cases of cryoglobulinemia or hematologic evidence to suggest that any of the men who developed cold injury had abnormal circulating proteins, plasma hyperviscosity, or indicators of alcohol abuse.

In the 1990s, both the U.S. Army and the Israel Defense Forces recorded that the majority of nonfreezing cold injuries occurred during routine training exercises, rather than during combat operations.

**ETHNICITY**

Historically, the first reports of increased susceptibility in certain ethnic groups (blacks) to cold-weather injury came from the American Civil War. It was also noted that there was an increased incidence of cold injuries among blacks in the cold winter conflict in the Ardennes in 1944 during World War II. A major retrospective study looking at 2143 U.S. Army cold-weather injury hospital admissions between 1980 and 1999 found that the injury rates for men and women were 13.9 and 13.3 per 100,000 soldiers, respectively. Increased rank and experience were associated with a decrease in cold-weather injuries. There were 3.5 times more blacks hospitalized than whites, (95% confidence interval [CI], 3.1-3.7), and infantry and gun crews appeared to be at greater risk. There was a marked reduction in the number of soldiers admitted to the hospital between 1980 and 1999, from greater than 30 cases per 100,000 soldier years to almost zero.

Young male African Caribbeans in the British Army have been found to have a 30 times greater chance of developing peripheral cold injury and are more severely affected than are their white counterparts following similar climatic exposure, using similar clothing and equipment. Pacific Islanders carry a 2.6 times increased risk, whereas being a Gurkha appears to be protective. Peripheral vascular responses to a local cold stress were studied in four groups of Indians: South Indians, North Indians, Gurkhas, and high-altitude natives of 3,500 meters (11,483 feet). The heat output and cold-induced vasodilation (CIVD) were highest in high-altitude natives, with the lowest observed in South Indians.

**PREVALENCE**

In most North Atlantic Treaty Organization (NATO) countries, prevalence of NFCI injuries appears to be static or decreasing among military personnel. However, in the British military, there appears to be a marked increase in the incidence of reported cold-weather injury. Over a 4-year period, the reported rate increased from 9 per 1000 to 30 per 1000 recruits, with the majority of cases (90%) originating during field-based training. Independent factor analysis demonstrated that African Caribbeans were 13.2 (95% CI, 9.5-18.4, probability [p] <0.01) times more likely to report cold injury and 27.3 (95% CI, 16.3-45.9, p <0.01) times more likely to be medically discharged than were whites. The rise in NFCI in the military of the United Kingdom (UK) may be caused by increased exposure, lower threshold to diagnose the condition, increased awareness, or recruiting of a different and more sensitive population. Alternatively, the rise may be caused by a type I statistical error (poor specificity of the tests used to diagnose NFCI or excessive credulity) or a type II error.

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The environmental conditions that can produce NFCI in military settings are also found in the context of wilderness medicine. Outdoor recreation may lead to cold, dehydrated, exhausted, and wet hikers exposed to the elements for an extended period. These individuals may be unwilling or unable to take the time and effort to care for their wet boots and socks, and they may be unaware of the risks inherent in the situation. Other civilian populations at risk for NFCI include the homeless, older adults, and alcoholics.

Personal Administration

Proper protective equipment and appropriate use are important factors reducing the incidence of NFCI. Factors affecting the incidence of frostbite are closely related to those affecting NFCI. A surprisingly high incidence of frostbite has been reported in mountaineers. In one study, the mean incidence was 366 per 1000 population per year. Mild (grade 1) injury (83.0%) and hand (26.4%) and foot (24.1%) involvement were most common. There was a significant relation between lack of proper equipment (odds ratio 14.3) or guide (p < 0.001) and the injury. Inappropriate clothing, lack or incorrect use of equipment, and lack of knowledge of how to deal with cold and severe weather were claimed to be the main reasons for the injury.

Cold injury is uncommon in Antarctica. Despite this, it warrants a continuing high profile, because under most circumstances, it may be regarded as an entirely preventable occurrence. It has been suggested that prolonged heavy load carriage during a 109-day Arctic expedition may have impaired blood flow or nerve conduction in the hands and inhibited cold acclimatization. However, a different response was observed in the feet, where there was improvement in cold acclimatization despite development of moderate trench foot.

Civilian Case Reports

Laden and colleagues reported cold injury to a diver’s hand after a 90-minute dive in 6°C (42.8°F) water. With the advent of “technical diving,” characterized by going deeper for longer periods of time, this may become more common. With external heating to maintain skin temperature at 41°C (105.8°F), this may increase to 7000 to 8000 mL/min, whereas cooling the skin to 14°C (57.2°F) may diminish it to 20 to 50 mL/min. Heat is dissipated by four processes: radiation, conduction, convection, and evaporation.

CUTANEOUS TISSUE damage is inversely related to ambient temperature. Cold-induced vasodilation is attenuated by α2-receptor blockers and by sympathetic inhibition. Reduction in ambient temperature results in insertion of more α2-receptors from the myocyte Golgi apparatus into the plasma membrane, raising affinity for the sympathetic neurotransmitter norepinephrine. At the same time, endothelial nitric oxide synthase (eNOS) activity declines, resulting in vasoconstriction of AVAs. Core temperatures have a strong influence over cutaneous sympathetic vasomotor activity.

Vascular endothelium regulates local vascular tone by secreting vasoactive agents, including the vasconstrictor endothelin and the vasodilators nitric acid and prostacyclin. Endothelin causes long-lasting vasoconstriction and is elevated in hypoxia, preeclampsia, and hemorrhagic stroke.

ORTHOSTASIS

Orthostasis causes immediate reduction in local blood flow. Indeed, cutaneous perfusion is reduced by approximately two-thirds as a result of the poorly understood arteriolar-venous response. It is believed that this response helps maintain central arterial pressure during standing and also reduces dependent edema formation. Long periods of sitting or standing tend to exacerbate this response.

COLD-INDUCED VASODILATION

When the hand or foot is cooled to 15°C (59°F), maximal vasoconstriction and minimal blood flow occur. If cooling continues to 10°C (50°F), vasoconstriction is interrupted by periods of vasodilation and an associated increase in blood and heat flow. This CIVD, or “hunting response,” occurs in 5- to 10-minute cycles to provide some protection from the cold. Prolonged repeated exposure to cold increases CIVD and offers some degree of acclimatization. Inuit, Sami, and Nordic fishermen have a very strong CIVD response and very short intervals between dilations, which may contribute to maintenance of hand function in the cold environment. CIVD responses are more pronounced when the body core and skin temperatures are warm (hyperthermic state) and suppressed when they are cold (hypothermic state), when compared with normothermia. Cheung and Mekjavic investigated whether CIVD responses of one finger can predict the responses of other fingers and also whether the CIVD of fingers could predict CIVD responses of the feet and toes. They found that CIVD is highly variable across the fingers and is not a generalizable response across either digits or limbs. Paradoxical CIVD will normally prevent tissue damage, but in conditions such as Raynaud’s disease, the vessels of the toes and fingers exhibit an exaggerated and sustained vasoconstriction response, resulting in blanching, numbness, and paresthesias and in severe cases tissue loss.

Subjects with a weak CIVD to experimental cold-water immersion of the fingers in a laboratory setting have been shown to have a higher risk for local cold injuries when exposed to cold in real life. There is a strong relationship between the mean temperature of the fingers during cold-water immersion and toes during cold-air exposure (correlation coefficient for bivariate analysis [r] = 0.83, p < 0.01), showing that a weak CIVD response in the hand correlates with a weak response in the foot. Pelicjjan and colleagues found evidence for significant enhancement of the CIVD response after brief high-altitude acclimatization and that these changes were especially prominent in the feet of Alpinists when compared with controls.

Temperatures of the extremities can drop surprisingly quickly in the field. Toe temperatures of 10 subjects were monitored in the field in Arctic Norway (minimum air temperature ~27°C [~16.6°F]). The lowest skin temperature recorded was 1.9°C (35.4°F). The mean estimated time for toe temperature to cool from 25°C (77°F) to 5°C (41°F) was 109 minutes (standard
Small-diameter nerves. The prolonged cold injury affects blood not mean that this exposure was without risk. 101 Subjects demonstrated clinical signs of cold injury, but this does not mean that this exposure was without risk. 101 The cutaneous microcirculation of skin was assessed in patients with sequelae from local cold injuries. All patients reported cold intolerance 3 to 4 years after the primary cold injury (sustained during military service). 102 The transcutaneous oxygen tension was decreased, but oxygen recovery index, postocclusive reactive hyperemia, and venoarterial reflex were normal. No capillary nailfold abnormalities were found. Local cold injuries appear to cause disturbances in the CIVD, impaired cold tolerance, and increase the risk for future cold injuries. There is evidence to suggest disturbances of reflex mechanisms mediated by the central nervous system, pathophysiologic factors seem more important than ischemic mechanisms in the pathophysiology of late sequelae with peripheral cold-weather injuries.

Trench Foot (Immersion Foot)
PATHOPHYSIOLOGY
Continuous exposure to a cold, wet environment causes skin breakdown, directly cools nerves in the area of exposure, and causes prolonged vasoconstriction. NFCI is primarily caused by prolonged vasoconstriction, which in turn causes direct injury to the vessels (and endothelium) that supply blood to nerves, fat, and muscle cells. 97 Pain, fear, constrictive footwear, and immobility interact in maintaining vasoconstriction through a heightened sympathetic nervous system response or by mechanically limiting blood flow (Figure 7-1). Nerve cooling has been suggested as a contributing factor in the development of NFCI. Large myelinated fibers (C fibers) are most susceptible to prolonged cold exposure. 51,61,62,63,64 In severe nonfreezing cold injury, there is characteristic peripheral nerve damage and tissue necrosis. 52,57 Clinical sensory tests indicate damage to both large- and small-diameter nerves. The prolonged cold injury affects blood vessels serving these large myelinated fibers, with subsequent ischemia causing decreased oxygen to the nerve, resulting in the appearance of a primary nervous system injury. 38,52 (Figures 7-2 to 7-5).

Vasoconstriction is mediated by presynaptic vesicle release of norepinephrine and neuropeptide Y from sympathetic nerve fibers that interact postsynaptically on smooth muscle at α and Y1 receptors. Recent work demonstrated that cold-induced vasoconstriction is mediated by Rho kinase. The prolonged decrease in blood flow caused by vasoconstriction causes direct injury to capillary endothelium. Studies indicate that the endothelial lining separates from underlying cells, leaving “gaps.” 31 Leukocytes and platelets fill in these gaps and accumulate to further decrease capillary blood flow, leading to ischemia and eventual tissue hypoxia (Figure 7-6, online). The degree and duration of cold exposure determine severity of the injury.

Animal models have been developed to understand the underlying pathophysiology of NFCI. Thomas and co-workers developed a rat model of NFCI by immersing the tail in 1 °C (33.8 °F) water for 6 to 9 hours and characterized the loss of CIVD and a prolonged decrease in tail blood flow followed by an increase in blood flow above baseline. This pattern is similar to that clinically observed in humans during the prehyperemic phase followed by the hyperemic phase. In rats, absence of CIVD with prolonged cold exposure is similar to this prominent and consistent finding of NFCI in humans.

Stephens and associates used the rat tail model in an attempt to elucidate possible mechanisms that cause vascular endothelial damage. Their preliminary data suggest that acute cold-water exposure causes loss of nitric oxide–dependent endothelial function and possibly a change in smooth muscle contractility. Using a rabbit hind limb model, Irwin demonstrated that cold-water immersion damaged large myelinated fibers while sparing small myelinated and unmyelinated fibers.

Nonfreezing cold injuries affect many different types of tissue. Pathologic examination of specimens displays a variety of lesions in skin, muscle, nerves, and bone. 97,98 Muscles exhibit separation of cells and damage to muscle fibers, described as acidophilic and hyalinized (Zenker's hyaline degeneration). The myoplasm within muscle loses its cross striation, and the healing muscle appears to undergo fibrous tissue replacements.

One of the major pathologic processes in cold injury is progressive microvascular thrombosis following reperfusion of the ischemic limb, with cold-damaged endothelial cells playing a central role in the outcome of these cold-injured tissues. 99 Reperfusion of previously ischemic tissues causes free radical formation, leading to further endothelial damage and subsequent edema. With restoration of blood flow, there is reintroduction of oxygen species within cells that further damages cellular proteins, DNA, and the plasma membrane. Free radical species may also act indirectly in redox signaling to initiate apoptosis. Leukocytes may accumulate in small capillaries, obstructing them and leading to more ischemia. 99

In an in vivo rabbit hind limb model subjected to 16 hours of cold immersion (1 ° to 2 °C [33.8 ° to 35.6 °F]), there was

FIGURE 7-2 Laser Doppler mean nerve blood flow (NBF) in control and experimental animals at 10-minute intervals during nerve cooling and rewarming (up to 250 minutes) and at follow-up examination immediately before sacrifice (at various times up to 5 days). Note that the nerve blood flow falls steeply over 20 minutes and reaches its nadir (25% of baseline) 180 minutes after the onset of cooling. Nerve blood flow remains significantly reduced up to 5 days after cold injury. (Modified from Jia J, Pollock M: The pathogenesis of non-freezing cold nerve injury: Observations in the rat, Brain 120:631, 1997.)
FIGURE 7-3 Sciatic nerve epineurial microvessels before, during, and following nerve cooling (1° to 5° C [33.8° to 41° F]). A, Normothermia. Arteriole (A), venule (V), and metarterioles (M) have a normal appearance. B, One hour after the commencement of nerve cooling the diameter of both the arteriole and venule are reduced by approximately 40%. Under a dissecting microscope, erythrocytes present a granular appearance in both vessels (arrows). Note occlusive aggregations (open arrow) in metarteriole and the suggestion of leukocyte clumping in the venule (arrow head). C, Two hours after nerve cooling, segmental occlusive aggregates are seen in the venule (arrows). The arterioles contain prominent rouleaux (open arrows). D, Three hours after nerve cooling, there is stasis of flow in both vessels. An occlusive aggregate (arrow) is now seen in the arteriole, and those in the venule have extended (open arrows). E, After 1 hour of nerve rewarming (37.5° C [99.5° F]), the venule still exhibits multiple segmental occlusions (arrows). Erythrocyte granulations (open arrows) in the arteriole indicate poor reperfusion. Bars represent 100 mm. (From Jia J, Pollock M: The pathogenesis of non-freezing cold nerve injury: Observations in the rat. Brain 120:631, 1997.)

FIGURE 7-4 Electron micrographs of endoneurial vessels in cooled sciatic nerve. A, An empty capillary with a degenerating pericyte 1 hour after nerve rewarming. Bar represents 2 μm. B, Aggregating platelets (arrows) 24 hours after cooling. Bar represents 2 μm. C, Platelets, adherent to the endothelium of a venule, show varying degrees of degranulation without pseudopod formation, 48 hours after nerve cooling. Two red blood cells are trapped within this platelet thrombus. Bar represents 1 μm. D, A thrombus formed of platelets, red blood cells, and fibrin 5 days after nerve cooling. The blood vessel wall is necrotic. Bar represents 2 μm. (From Jia J, Pollock M: The pathogenesis of non-freezing cold nerve injury: Observations in the rat, Brain 120:631, 1997.)
sensation has been described as “walking on air” or “walking on
prioception, resulting in numbness and gait disturbances. This
the cold sensation leads to complete anesthesia with loss of pro-
feet although hands can also be affected. With further exposure,
local anesthesia, which is distinct from premonitory feelings of

criterion is loss of a sensory modality, most typically complete
is exposed to cold and wet conditions at temperatures ranging
pools, turning the extremity a deep purple-red color, whereas
reduction in the number of myelinated nerve fibers of all sizes,
most marked in large-diameter fibers, a feature consistent with
ischemic neuropathy and reperfusion injury. Unmyelinated
fibers showed only minor damage. The resulting evidence has
suggested that both of these mechanisms may contribute to the
type of nerve damage. Both these studies used models that assumed that cold-induced
nerve injury, rather than capillary or endothelial damage, is the
primary cause of NFCI.

CLINICAL PRESENTATION

Trench foot and immersion foot are clinically and pathologically
indistinguishable but have different etiologies. The term trench foot originated during the trench warfare of World War I, when soldiers wore wet boots and socks for prolonged periods. Immersion foot was first medically documented during World War II among shipwreck survivors whose feet had been continuously immersed in cold water. Both injuries occur when tissue is exposed to cold and wet conditions at temperatures ranging from 0°C to 15°C (32°F to 59°F). Colder temperatures decrease the
time required to induce NFCI. Severe nerve damage from
immersion foot has been seen after exposure periods of 14 to
22 hours. Immersion foot injury may extend proximally and
involve the knees, thighs, and buttocks, depending on the depth
of immersion. Clinically, NFCI is insidious in onset, with progress-
ion from initial exposure through three distinctive phases
(prehyperemic, hyperemic, posthyperemic). These phases have
variable time courses and may overlap.

Prehyperemic Phase

During the prehyperemic phase, the affected limb, both during
and immediately after cold exposure, appears blanched, yellowish
white, or mottled but seldom blistered (Figure 7-7). Whayne and
DeBakey state that the degree of edema during this prehyper-
emic stage is less severe if the feet are intermittently rewarmed
during the course of exposure. Whereas muscle cramps are
common, pain is rare. The single most important diagnostic
criterion is loss of a sensory modality, which is distinct from premonitory feelings of
extreme cold in the affected periphery, almost invariably in the
feet although hands can also be affected. With further exposure,
the cold sensation leads to complete anesthesia with loss of pro-
prcoception, resulting in numbness and gait disturbances. This
sensation has been described as “walking on air” or “walking on
cotton wool.” Capillary refill is sluggish, and pedal arterial pulses
are usually absent, except through Doppler examination. Intense
vasoconstriction is the predominant feature of this stage.

Hyperemic Phase

Within several hours after rewarming, the extremities become
hot, erythematous, painful, and swollen (Figures 7-8 to 7-11; Figure 7-9, online), with full bounding pulses. Impairment of
the microcirculation is evident through delayed capillary refill
(Figure 7-12, online) and petechial hemorrhages. Sensation
returns first to proximal regions and then extends distally, rapidly
progressing to a severe, burning, or throbbing pain and reaching
maximal intensity in 24 to 36 hours. Ached areas have
marked hyperalgesia to light touch. This pain is aggravated by
heat and dependent positioning and often worsens at night,
when even the pressure of sheets may become unbearable. After 7 to 10 days, the nature of the pain changes to “shooting or
stabbing.” The sensory deficits usually diminish, but pares-
thesias continue, and anesthesia may be extensive on the toes
and plantar foot surfaces. Vibratory sensation is reduced or
lost, whereas proprioception is usually retained. Anhidrosis coin-
cides with the extent of sensory loss.

Vascular injury is evident in vessel reactivity. Skin temperature
gradients are absent, with digits often as warm or warmer than
the groin or axillae. When the affected limbs are lowered, blood
dolors, turning the extremity a deep purple-red color, whereas

FIGURE 7-5 Electron micrographs of cooled sciatic nerve fibers. A, A rat sciatic nerve fiber, 12 hours after nerve cooling, illustrating myelin
unraveling and intramyelinic edema (arrow). B, A rat sciatic nerve fiber 2 days after cooling, exhibiting a shrunken axon and marked periaxonal edema. Bars represent 1 μm. (From Jia J, Pollock M: The pathogenesis of non-freezing cold nerve injury: Observations in the rat, Brain 120:631, 1997.)

FIGURE 7-7 Prehyperemic phase of immersion foot. These feet are still mostly numb and very cold to the touch. (British Crown Copyright/ MOD.)
blanching occurs when the limb is raised. Tense edema becomes marked during this stage. Blisters containing serous or hemorrhagic fluid may form, indicating more severe injury. The superficial epidermis becomes thick, indurated, and desquamated. Eschars form (Figures 7-13 and 7-14) and eventually slough, leaving a pink dermis (Figure 7-15). In more severe cases, the skin may become gangrenous (Figure 7-16). This is rare, and with appropriate care, gangrene is usually minimal.

Muscles may show weakness with impaired electrical responses, slowing of plantar deep tendon reflexes, and intrinsic muscle atrophy. In milder cases, this stage peaks at 24 hours; in more severe cases, the hyperemic phase may take 6 to 10 weeks to resolve.

**Posthyperemic Phase**

The posthyperemic phase lacks obvious physical signs. In mild cases, this phase may be absent; in other cases, it may last weeks, months, or years after the hyperemic phase has subsided. The extremities transition from a consistent warmth to noted coolness, with affected areas becoming cold sensitive, remaining so for hours after exposure despite normal warming processes.

After 6 to 10 weeks, patients often complain of spontaneous hyperhidrosis, and sweat rashes are common in areas with heavy perspiration. On a warm day, socks are quickly soaked; extremities may sweat excessively, even when cold. Hyperhidrosis predisposes to chronic paronychial infections. Sweating may be more pronounced at the margins of anhidrotic and analgesic areas.

During the posthyperemic phase, the paresthesias and extreme pains typical of the hyperemic phase have usually resolved, replaced by dull aches and anesthesia that may persist for months to years. Recurrent edema of the feet, return of paresthesia,
and further blistering are common, especially after long walks. Intrinsic muscle and ligament atrophy tend to resolve, but in severe cases, fibrous scarring may lead to rigidity and permanent contracture of the toes. Decalcification of bones similar to that seen with osteoporosis is frequently observed. Immobility and pain in severe cases may lead to prolonged convalescence of 6 or more months.

In the most severe cases, gangrene can develop, and ablative surgery in the form of amputations of digits or even major lower limb amputation becomes necessary. Neuropathic tissue is susceptible to local trauma, ulceration, and eventually local osteomyelitis and sinus development. Appearance and behavior of the neuropathic foot have many similarities to those of the diabetic foot. In the diabetic foot, infections tend to be polymicrobial with *Staphylococcus aureus*, *Staphylococcus epidermidis*, and *Enterococcus* and *Streptococcus* species being most commonly isolated from bone culture. However, aerobic gram-negative rods (such as *Pseudomonas aeruginosa*) and obligate anaerobic species may be found. Partial foot amputations may result in significant alterations in functional biomechanics of the foot. Because this is often associated with alterations in the sensory nerve supply to the feet, ongoing disabling problems can persist (Figure 7-20).

**More Severe Injuries**

NFCl can vary in severity from mild to severe. In severe cases, cold sensitization is so serious that individuals are unable to work outside. There is often persisting edema and hyperhidrosis, making the individual susceptible to fungal infections. Chronic pain may resemble causalgia or reflex sympathetic dystrophy. The profound sensory neuropathic foot can develop ulcerations and tissue loss, ultimately resulting in either minor or major lower limb amputation. Ongoing care with a foot specialist who can arrange for custom-made shoes and insoles appears to improve functional outcome. Multidisciplinary team approaches to coordinating care leading to healing of the ulcerated neuropathic foot using patella weight-bearing orthoses has been described. NFCI pain is often so severe as to require tricyclic antidepressants, which may need to be instituted at an early stage. Failure to do so increases the risk for developing severe chronic pain resistant to all subsequent treatment modalities. Early involvement of
The affected extremities should never be rubbed, which can worsen pain, reduce circulation, and hasten collagen and fibrous tissue absorption. In severe cases of NFCI exhibiting atrophic rigid feet, small case studies have shown symptomatic improvement after sympathectomy, but other clinicians feel that there is little therapeutic advantage to the procedure.

**Tissue-Freezing Complications**

Frostbite and NFCI injuries do not necessarily occur in isolation, and when assessing an individual, both diagnoses need to be entertained. Following exposure to severe cold, careful appraisal of the injury allows selection of optimal treatment.

**Drugs**

Diagnosis of NFCI is often difficult or delayed. In view of involvement of the $\alpha$-receptors in the control of peripheral circulation and the apparent noradrenergic sensitization, it was believed that vasodilators or $\alpha$-blocking drugs might be beneficial. However, there is no evidence to support this approach.

Because painful rewarming and persistent pain are features of NFCI, it is important to attempt to alleviate pain at an early stage. Although simple analgesics may be of benefit, Thomas and Oakley observed that quinine sulfate (200 to 400 mg, given at night) appeared more successful than regular analgesics, although others have since commented that they are not useful. Since 1982, the standard treatment in the United Kingdom, first proposed by Riddell, has been amitriptyline hydrochloride, in doses of 50 to 100 mg given at night. Incremental increases in dosage may be required with both drugs if pain breaks through after initial relief.

**ASSESSING THE SEVERITY OF NONFREEZING COLD-INDUCED INJURY**

Following the initial injury, there develops increased sensitivity to cold. There are often few objective clinical signs of a nonfreezing cold injury. A careful history of cold exposure, clear history of the typical rewarming symptoms and signs, detailed examination, and special investigations combine to build a case consistent with NFCI. Corroborative evidence of an appropriate cold exposure and symptoms consistent with NFCI from medical records is vital.

**Special Investigations**

Infrared thermography can be used to assess the individual’s response to a standardized cold stress and may be helpful in confirming the diagnosis, assessing the severity of injury, and monitoring recovery from NFCI (Figure 7-21). Although the infrared thermography test is used extensively by the UK military, it is not widely used elsewhere. There appears to be significant intranormal variability in the responses of some individuals to the current infrared thermography test. As a result, interest is shown in the use of gentle exercise before the infrared thermography cold sensitivity test and also in the use of laser Doppler flowmetry to try to improve the assessment used to classify nonfreezing cold injury.

**PREVENTION**

The simplest way to prevent NFCI is to avoid prolonged exposure to cold, wet environments. This can be difficult to achieve. During military conflict, completing the assigned mission may require performing in a cold, wet environment for sustained periods of time in cramped, immobile positions. During mountain rescues, individuals may be so focused on helping to save others that they do not take adequate care to prevent NFCI.

Prevention can be achieved by encouraging activities that promote blood flow to the feet, rotating personnel out of cold, and increasing endothermic cell injury, coupled with reflex vasodilation, lead to fluid transudation, increasing edema, skin necrosis, and worsening pain. In severe cases of NFCI exhibiting atrophic rigid feet, small case studies have shown symptomatic improvement after sympathectomy, but other clinicians feel that there is little therapeutic advantage to the procedure.

**Rewarming**

Treatment is limited to symptomatic relief and reversing ischemia while minimizing progression of disease. Rewarming injured tissues increases metabolic demand of damaged cutaneous cells to a greater extent than can be provided by the supply capability of the injured subcutaneous blood vessels. Tissue anoxia and endothelial cell injury, coupled with reflex vasodilation, lead to fluid transudation, increasing edema, skin necrosis, and worsening pain.
least 8 hours out of every 24. Vapor-barrier boots do not meet military suggestions that optimal care entails air drying feet for at least 8 hours out of every 24. Changing of wet socks, maintaining core body temperature by methods such as staying in a warm barracks, and by educating people about the early signs and symptoms of wet environments on a regular basis, keeping feet dry by early recognition. Well-designed equipment, supplied to appropriate personnel, and used in a timely and appropriate way should reduce the incidence of injury. The severity of current UK military NFCI events appears to be relatively mild in comparison with civilian NFCI injuries (see Figures 7-17 to 7-19) and military historical controls (see Figures 7-13 to 7-16). This raises the question of whether (1) there is a continuous spectrum of disease, (2) there is a bimodal distribution of the disease with milder and more severe forms of NFCI, or (3) the commonly presenting form is the same disease process that has been investigated in the past. Perhaps the lack of clarity lies in the UK military's decision to use infrared thermography as one of the bases for diagnosis, severity, and progression of NFCI. There appears to be a lack of published control data on subjects' prior response to cold exposure, so that the test cannot be compared with the normal variability in the population. One approach would be to screen potential recruits. This requires a test with high sensitivity and specificity. However, individual variation in the control of peripheral blood flow is so great that no assessment currently available meets these requirements. Reducing the incidence of cold injury in military training requires striking a delicate balance between training, realism, and safety. Training in demanding environments runs real risks of injuring personnel, but the benefits to soldiers in their necessary field skills are vital if they are to avoid future NFCI.

### Pernio (Chilblains)

Pernio (perniones), or chilblains, are localized, inflammatory, bluish red lesions caused by an abnormal reaction to a cold, damp environment. This mild form of cold injury is prevalent in the temperate climates of northwestern Europe, and it is found worldwide throughout temperate and northern zones. Pernio is less common in very cold climates where well-heated houses and adequate warm clothing are common. In a study of 111 patients, 67 (60.4%) were males and 44 (39.6%) were females. Eighty-nine (80.2%), 90 (81.1%), and 90 (81.1%) patients had onset in relation to lower temperature (<10°C [50°F]), relatively low atmospheric pressure (<1500 kPa), and higher relative humidity (>60%), respectively. Susceptibility to chilblains appeared to increase when ambient temperature was less than 10°C (50°F) and relative humidity more than 60%. Acute pernio has a seasonal incidence, with reversible symptoms more common in cold weather. The acute form is seen primarily in schoolchildren and young adults under the age of 20 years, with the highest incidence in adolescent females. It can occur in mildly cold settings such as logging, kayaking, snowmaking, winter horseback riding, and hiking. Pernio can be caused by brief (30 minutes) cold exposure, often appearing several hours after exposure, with the skin lesions fully developed within 12 to 24 hours. Characteristic locations for these lesions are the feet, hands, legs, and thighs. Single or multiple, erythematous, purplish, edematous lesions form, with vesicles in severe cases. Symptoms include intense pruritus, burning, or pain, often worsened by subsequent warmth. The lesions of acute pernio are self-limited and usually resolve within a few days to 3 weeks, occasionally leaving residual hyperpigmentation. Although the healing process appears to occur as the plaques resolve, pain often persists. Subsequent mild cold exposure may trigger paresthesias, edema, and skin scaling.

Chronic perniosis usually progresses over several winters after repeated episodes of acute pernio, rarely progressing from the initial injury to chronic irreversible skin changes within a single season. Repeated episodic seasonal lesions may become edematous, with permanent discoloration and subcutaneous nodules forming. The nodules are firm and painful, ultimately rupturing and providing pain relief and leaves a shallow ulcer with pigmented atrophic skin. These ulcers may grow larger and coalesce, remaining open, which leads to permanently swollen extremities, scaly pigmented skin, and unremitting pain aggravated by light pressure.

Pernio is believed to be caused by prolonged cold-induced vasospasm with subsequent hypoxemia and vessel wall inflammation. Subcutaneous arterial vasoconstriction is documented by both pathologic and arteriographic studies. Histologic examinations show a lymphocytic vasculitis and papillary dermal edema with pervasive inflammatory changes. The differential diagnosis includes lupus erythematosus, Raynaud’s disease, polycythemia vera, arteriomatic embolization, erythema nodosum, and livedo vasculitis with ulcerations.
Treatment of pernio is accomplished by drying and gently massaging the affected skin. Active warming above 30°C (86°F) significantly worsens the pain and should be avoided.46 Although therapeutic regimens in the literature include nicotinic acid,52 ultraviolet irradiation,48 thymoxamine,59 intravenous calcium combined with intramuscular vitamin K,54 corticosteroids,59 and sympathectomy in severe cases,60 few have proved to be either effective or universally accepted. Recently, nifedipine (20 mg, 3 times daily) has been shown to be effective for treatment of severe pernio.51,126 Preventing pernio is relatively simple. Recommended prophylactic measures include minimizing cold exposure with suitable clothing when outdoors and maintaining adequate warm temperatures indoors.

Cryoglobulinemia

Cryoglobulins are cold-precipitable serum immunoglobulins.96 These cryoglobulins were first reported in a patient with multiple myeloma15 and were subsequently recognized to occur in a diverse group of hematologic malignancies, acute and chronic infections, and collagen vascular diseases.94-106 Cryoglobulins are classified as three types. Type I cryoglobulins (10% to 15% of total) are composed of a monoclonal immunoglobulin, primarily IgG. Type II cryoglobulins (50% to 60% of total) are polyclonal, most frequently IgG and IgM. The IgM fraction usually has rheumatoid factor activity. Type III cryoglobulins (25% to 30% of total) are also composed of polyclonal IgG and IgM fractions.

There are many clinical conditions that are associated with cryoglobulinemia.96 Infections (viral, bacterial, fungal, parasitic), hematologic diseases (chronic lymphocytic leukemia, multiple myeloma), and autoimmune diseases (rheumatoid arthritis, pulmonary fibrosis, inflammatory bowel disease) are all associated with cryoglobulinemia. Hepatitis C is considered a principal trigger of cryoglobulinemia. Serum cryoglobulin values do not usually correlate with the severity of the disease, but may serve as a marker of the disease.

Cryoglobulinemia is characterized by a clinical triad of purpura, weakness, and arthralgias. A large clinical trial showed that two-thirds of patients diagnosed with cryoglobulinemia initially presented with symptoms of skin lesions or Raynaud’s disease—like vasomotor attacks. Mucosal bleeding, visual disturbances, and abdominal pain were less common, and Raynaud’s phenomenon was apparent in less than one-half of these patients.53 Symptoms associated with cryoglobulins include typical Raynaud’s phenomenon, dependent purpura, cutaneous vasculitis with ulceration, retinal hemorrhages, coagulopathies, glomerulonephritis, renal failure, and cerebral thrombosis.

Treatment of cryoglobulinemia should be directed at the severity of the symptoms and to the disease causing the cryoglobulinemia. Because hepatitis C virus (HCV) is implicated in many cases of types II and III cryoglobulinemia, targeting HCV is the treatment of choice to eliminate cryoglobulinemia. Interferon, prednisone, and ribavirin have all been used to treat HCV and associated cryoglobulinemia. For non–HCV-associated cryoglobulinemia with mild to moderate symptoms (purpura, arthropathy, sensory neuropathy), immunosuppression with corticosteroids and analgesics is the treatment of choice.58 A low-antigencontent diet (rice, fresh vegetables, fruit, tea) has been shown to improve purpura.51 With severe manifestations of disease such as renal failure, neurologic impairment, disabling paresthesias or myalgias, plasmapheresis may be helpful in reducing the cryoimmunoglobulin concentration below a critical point to alleviate symptoms.38 Plasmapheresis is used in conjunction with corticosteroids or other drugs, because discontinuing plasmapheresis treatment usually causes reappearance of the cryoglobulinemia.96

Cold Urticaria

Cold urticaria is a physical urticaria characterized by development of either localized or generalized wheals and itching after skin exposure (air, liquid, object) to cold89 (Figure 7-22). It most frequently affects young adults with a duration of 4 to 5 years, although primary cold urticaria can occur at any age. Women are twice as likely to be affected.89 The incidence rate is approximately 0.05% of the population.

Symptoms are usually limited to cold-exposed skin areas.89 Local symptoms include redness, itching, wheals, or edema of the exposed skin. These wheals last approximately 30 minutes. Systemic reactions can also occur, and symptoms of this include fatigue, headache, dyspnea, and hypotension. Swimming in cold water is the most common trigger of severe reactions. This may lead to hypotension, fainting, shock, and possibly death.7,45 Sufocation may also occur after consuming cold drinks as a result of pharyngeal angioedema.89

Secondary urticaria occurs in 5% of patients with cold urticaria.95 The wheals are more persistent and may be associated with purpura and vasculitis on skin biopsy. This disorder is associated with an underlying disorder such as cryoglobulinemia, cold agglutinins, paroxysmal hemoglobinuria, or connective tissue disease.107 In addition, there is a rare autosomal dominant familial form that has its onset in infancy and is associated with arthralgias and leukocytosis.108

The cause of cold urticaria is unknown. Cold urticaria has been associated with viral or bacterial infections,5,59 as well as infections of the upper respiratory tract, teeth, and urogenital tract. It has been reported to involve the release of histamine,50 leukotrienes, and other mast-cell mediators,50 possibly mediated by IgE and IgM. Support for an IgE-mediated mechanism comes from successful treatment15 using an anti-IgE (omalizumab). The diagnosis of cold urticaria is made through the ice cube test in the majority of patients, in which a hive is induced by holding an ice cube to skin for 3 to 5 minutes. If the results are equivocal, a cold-water immersion test of submerging a forearm for 5 to 15 minutes in water at 0°C to 8°C (32°F to 46.4°F) establishes the diagnosis.

Treating cold urticaria with antihistamines is the most effective option. However, to sufficiently reduce symptoms may require dosing up to four times the recommended dose.5,59 In addition, other therapies include leukotriene antagonists, cyclosporine, corticosteroids, and anti-IgE.59 Individuals with severe reactions should have an emergency kit containing corticosteroids, antihistamines, and epinephrine. Based on the finding that infectious disease may be a trigger for cold urticaria, earlier treatment with antibiotics for infectious diseases may also be warranted.59

REFERENCES

Complete references used in this text are available online at www.expertconsult.com.