462 Altitude Illness

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EPIDEMIOLOGY

Mountains cover one-fifth of the earth's surface; 140 million people live permanently at altitudes ≥2500 m, and 100 million people travel to high-altitude locations each year. Skiers in the Alps or Aspen; tourists to La Paz, Ladakh, or Lahsa; religious pilgrims to Kailash-Manasarovar or Gosainkunda; trekkers and climbers to Kilimanjaro, Aconcagua, or Everest; miners working in high-altitude sites in South America; and military personnel deployed to high-altitude locations are all at risk of developing acute mountain sickness (AMS), high-altitude cerebral edema (HACE), high-altitude pulmonary edema (HAPE), and other altitude-related problems. AMS is the benign form of altitude illness, whereas HACE and HAPE are life-threatening. Altitude illness is likely to occur above 2500 m but has been documented even at 1500–2500 m. In the Mount Everest region of Nepal, ~50% of trekkers who walk to altitudes >4000 m over ≥5 days develop AMS, as do 84% of people who fly directly to 3860 m. The incidences of HACE and HAPE are much lower than that of AMS, with estimates in the range of 0.1–4%. Finally, reentry HAPE, which in the past was generally limited to highlanders (long-term residents of altitudes >2500 m) in the Americas, is now being seen in Himalayan and Tibetan highlanders—and often misdiagnosed as a viral illness—as a result of recent rapid air, train, and motorable-road access to high-altitude settlements.

PHYSIOLOGY

Ascent to a high altitude subjects the body to a decrease in barometric pressure that results in a decreased partial pressure of oxygen in the inspired gas in the lungs. This change leads in turn to less pressure, driving oxygen diffusion from the alveoli and throughout the oxygen cascade. A normal initial "struggle response" to such an ascent includes increased ventilation—the cornerstone of acclimatization—mediated by the carotid bodies. Hyperventilation may cause respiratory alkalosis and dehydration. Respiratory alkalosis may be extreme, with an arterial blood pH of >7.7 (e.g., at the summit of Everest). Alkalosis may depress the ventilatory drive during sleep, with consequent periodic breathing and hypoxemia. During early acclimatization, renal suppression of carbonic anhydrase and excretion of dilute alkaline urine combat alkalosis and tend to bring the pH of the blood to normal. Other physiologic changes during normal acclimatization include increased sympathetic tone; increased erythropoietin levels, leading to increased hemoglobin levels and red blood cell mass; increased tissue capillary density and mitochondrial numbers; and higher levels of 2,3-bisphosphoglycerate, enhancing oxygen utilization. Even with normal acclimatization, however, ascent to a high altitude decreases maximal exercise capacity (by ~1% for every 100 m gained above 1500 m) and increases susceptibility to cold injury due to peripheral vasoconstriction. If the ascent is made faster than the body can adapt to the stress of hypobaric hypoxemia, altitude-related disease states can result.

GENETICS

Hypoxia-inducible factor, which acts as a master switch in high-altitude adaptation, controls transcriptional responses to hypoxia throughout the body and is involved in the release of vascular endothelial growth factor (VEGF) in the brain, erythropoiesis, and other pulmonary and cardiac functions at high altitudes. In particular, the gene *EPAS1*, which codes for transcriptional regulator hypoxia-inducible factor 2α, appears to play an important role in the adaptation of Tibetans living at high altitude, resulting in lower hemoglobin concentrations than are found in Han Chinese or South American highlanders. Other genes implicated include *EGLN1* and *PPARA*, which are also associated with hemoglobin concentration. Some evidence indicates that these genetic changes occurred within the past 3000 years, which is very fast in evolutionary terms. An intriguing question is whether the Sherpas' well-known mountain-climbing ability is partially attributable to their Tibetan ancestry, with overrepresentation of variants of *EPAS*. A striking recent finding is that some of these genetic characteristics may stem from those of Denisovan hominids who were contemporaries of the Neanderthals.

For acute altitude illness, a single gene variant is unlikely to be found, but differences in the susceptibility of individuals and populations, familial clustering of cases, and a positive association of some genetic variants all clearly support a role for genetics.

ACUTE MOUNTAIN SICKNESS AND HIGH-ALTITUDE CEREBRAL EDEMA

AMS is a neurologic syndrome characterized by nonspecific symptoms (headache, nausea, fatigue, and dizziness), with a paucity of physical findings, developing 6–12 h after ascent to a high altitude. AMS is a clinical diagnosis. For uniformity in research studies, the Lake Louise Scoring System, created at the 1991 International Hypoxia Symposium, is generally used without the sleep disturbance score. AMS must be distinguished from exhaustion, dehydration, hypothermia, alcoholic hangover, and hyponatremia. AMS and HACE are thought to represent opposite ends of a continuum of altitude-related neurologic disorders. HACE (but not AMS) is an encephalopathy whose hallmarks are ataxia and altered consciousness with diffuse cerebral involvement but generally without focal neurologic deficits. Progression to these signal manifestations can be rapid. Papilledema and, more commonly, retinal hemorrhages may develop. In fact, retinal hemorrhages occur frequently at ≥5000 m, even in individuals without clinical symptoms of AMS or HACE.

Risk Factors The most important risk factors for the development of altitude illness are the rate of ascent and a prior history of high-altitude illness. Exertion is a risk factor, but lack of physical fitness is not. An attractive but still speculative hypothesis proposes that AMS develops in people who have inadequate cerebrospinal capacity to buffer the brain swelling that occurs at high altitude. Children and adults seem to be equally affected, but people >50 years of age may be less likely to develop AMS than younger people. In general, there is no gender difference in AMS incidence. Sleep desaturation—a common phenomenon at high altitude—is associated with AMS. Debilitating fatigue consistent with severe AMS on descent from a summit is an important risk factor for death in mountaineers. A prospective study involving trekkers and climbers who ascended to altitudes between 4000 and 8848 m showed that high oxygen desaturation and low ventilatory response to hypoxia during exercise are independent predictors of severe altitude illness. However, because there may be a large overlap between groups of susceptible and nonsusceptible individuals, accurate cutoff values are hard to define. Prediction is made more difficult because the pretest probabilities of HAPE and HACE are low. Neck irradiation or surgery damaging the carotid bodies, respiratory tract infections, and dehydration appear to be other potential risk factors for altitude illness. Unless guided by clinical signs and symptoms, pulse oximeter readings alone on a trek should not be used to predict AMS.

Pathophysiology Hypobaric hypoxia is the main trigger for altitude illness. In established AMS, raised intracranial pressure, increased sympathetic activity, relative hypoventilation, fluid retention and redistribution, and impaired gas exchange have all been well noted; these factors may play an important role in the pathophysiology of AMS. Severe hypoxemia can lead to a greater than normal increase in cerebral blood flow. However, the exact mechanisms underlying AMS and HACE are unknown. Evidence points to a central nervous system process. MRI studies have suggested that vasogenic (interstitial) cerebral edema is a component of the pathophysiology of HACE. In the

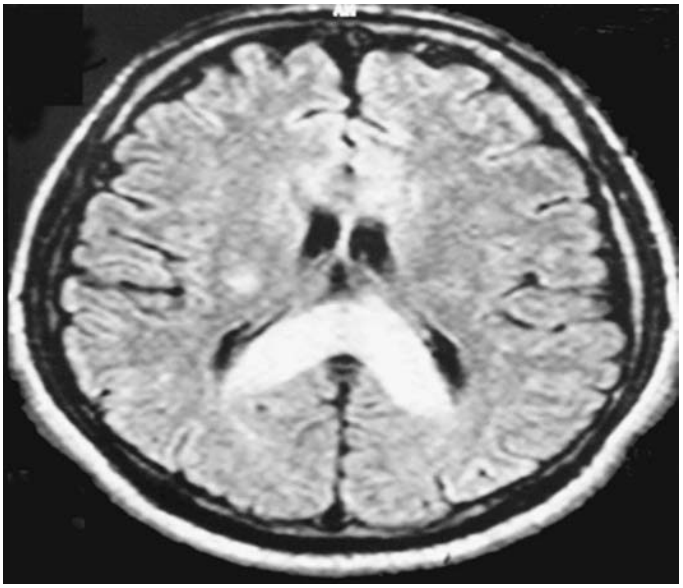

FIGURE 462-1 T2 magnetic resonance image of the brain of a patient with high-altitude cerebral edema (HACE) shows marked swelling and a hyperintense posterior body and splenium of the corpus callosum (area with dense opacity). The patient, a climber, went on to climb Mount Everest about 9 months after this episode of HACE. *(Source: FJ Trayers 3rd: Wilderness preventive medicine. Wilderness Environ Med 15:53, 2004.)*

setting of high-altitude illness, the MRI findings shown in Fig. 462-1 are confirmatory of HACE, with increased signal in the white matter and particularly in the splenium of the corpus callosum. In addition, hemosiderin deposits in the corpus callosum have been characterized as long-lasting footprints of HACE. Quantitative analysis in an MRI study revealed that hypoxia is associated with mild vasogenic cerebral edema irrespective of AMS. This finding is in keeping with case reports of suddenly symptomatic brain tumors and of cranial nerve palsies without AMS at high altitudes. Vasogenic edema may become cytotoxic (intracellular) in severe HACE.

Impaired cerebral autoregulation in the presence of hypoxic cerebral vasodilation and altered permeability of the blood-brain barrier due to hypoxia-induced chemical mediators like histamine, arachidonic acid, and VEGF may all contribute to brain edema. In 1995, VEGF was first proposed as a potent promoter of capillary leakage in the brain at high altitude, and studies in mice have borne out this role. Although studies of VEGF in climbers have yielded inconsistent results regarding its association with altitude illness, indirect evidence of a role for this growth factor in AMS and HACE comes from the observation that dexamethasone, when used in the prevention and treatment of these conditions, blocks hypoxic upregulation of VEGF. Other factors in the development of cerebral edema may be the release of calcium-mediated nitric oxide and neuronally mediated adenosine, which may promote cerebral vasodilation. Venous outflow obstruction resulting in increased brain capillary pressure is also thought to play an important role in the development of HACE. Lesions in the globus pallidum (which is sensitive to hypoxia) leading to Parkinson's disease have been reported to be complications of HACE.

The pathophysiology of the most common and prominent symptom of AMS—headache—remains unclear because the brain itself is an insensate organ; only the meninges contain trigeminal sensory nerve fibers. The cause of high-altitude headache is multifactorial. Various chemicals and mechanical factors activate a final common pathway, the trigeminovascular system. In the genesis of high-altitude headache, the response to nonsteroidal anti-inflammatory drugs and glucocorticoids provides indirect evidence for involvement of the arachidonic acid pathway and inflammation.

Prevention and Treatment (Table 462-1) Gradual ascent, with adequate time for acclimatization, is the best method for the prevention of altitude illness. Even though there may be individual variation in the rate of acclimatization, a conservative approach would be a graded ascent of ≤300 m from the previous day's sleeping altitude above 3000 m, and taking every third day of gain in sleeping altitude as an extra day for acclimatization is helpful. Spending one night at an intermediate altitude before proceeding to a higher altitude may enhance acclimatization and attenuate the risk of AMS. Another protective factor in AMS is high-altitude exposure during the preceding 2 months; for example, the incidence and severity of AMS at 4300 m are reduced by 50% with an ascent after 1 week at an altitude ≥2000 m rather than with an ascent from sea level. However, regarding the benefits of acclimatization, clear-cut randomized studies are lacking. Repeated exposure at low altitudes to hypobaric or normobaric hypoxia is termed *preacclimatization*. Preacclimatization is gaining popularity. For example, many Everest climbers in the spring of 2019 claimed to use commercially available "tents" at home with a hypoxic environment for weeks to months in preparation for the climb. However, the optimal method based on robust studies for preacclimatization is yet to be determined.

Clearly, a flexible itinerary that permits additional rest days will be helpful. Sojourners to high-altitude locations must be aware of the symptoms of altitude illness and should be encouraged not to ascend further if these symptoms develop. Any hint of HAPE (see below) or HACE mandates descent. Proper hydration (but not overhydration) in high-altitude trekking and climbing, aimed at countering fluid loss due to hyperventilation and sweating, may play a role in avoiding AMS. Pharmacologic prophylaxis at the time of travel to high altitudes is warranted for people with a history of AMS or when a graded ascent and acclimatization are not possible—e.g., when rapid ascent is necessary for rescue purposes or when flight to a high-altitude location is required. Acetazolamide is the drug of choice for AMS prevention. It inhibits renal carbonic anhydrase, causing prompt bicarbonate diuresis that leads to metabolic acidosis and hyperventilation. Acetazolamide (125 mg twice daily), administered for 1 day before ascent and continued for about 3 days at the same altitude, is effective. Treatment can be restarted if symptoms return after discontinuation of the drug.

TABLE 462-1 Management of Altitude Illness

CONDITION	MANAGEMENT
Acute mountain sickness (AMS), mild[a]	Discontinuation of ascent Treatment with acetazolamide (250 mg q12h) Descent[b]
AMS, moderate[a]	Immediate descent for worsening symptoms Use of low-flow oxygen if available Treatment with acetazolamide (250 mg q12h) and/or dexamethasone (4 mg q6h)[c] Hyperbaric therapy[d]
High-altitude cerebral edema (HACE)	Immediate descent or evacuation Administration of oxygen (2–4 L/min) Treatment with dexamethasone (8 mg PO/IM/IV; then 4 mg q6h) Hyperbaric therapy if descent is not possible
High-altitude pulmonary edema (HAPE)	Immediate descent or evacuation Minimization of exertion while patient is kept warm Administration of oxygen (4–6 L/min) to bring O_2 saturation to >90% Adjunctive therapy with nifedipine[e] (30 mg, extended-release, q12h) Hyperbaric therapy if descent is not possible

[a]Categorization of cases as mild or moderate is a subjective judgment based on the severity of headache and the presence and severity of other manifestations (nausea, fatigue, dizziness). [b]No fixed altitude is specified; the patient should descend to a point below that at which symptoms developed. [c]Acetazolamide treats and dexamethasone masks symptoms. For prevention (as opposed to treatment) of AMS, 125 mg of acetazolamide q12h or (when acetazolamide is contraindicated—e.g., in people with a history of sulfa anaphylaxis) 4 mg of dexamethasone q12h may be used. [d]In hyperbaric therapy (Fig. 462-2), the patient is placed in a portable altitude chamber or bag to simulate descent. [e]Nifedipine at this dose is also effective for the prevention of HAPE, as are tadalafil (10 mg twice daily), sildenafil (50 mg three times per day), and dexamethasone (8 mg twice daily). Preventative therapy should be continued for about 3 days after arriving at the target altitude. If prompt descent follows arrival at target altitude, continuation of preventative therapy is unnecessary.

Higher doses are not required. A meta-analysis limited to randomized controlled trials revealed that 125 mg of acetazolamide twice daily was effective in the prevention of AMS, with a relative-risk reduction of ~48% from values obtained with placebo. Even lower doses (62.5 mg twice daily) have been reported to be effective. Paresthesia and a tingling sensation are common side effects of acetazolamide. Some other uncommon side effects are myopia and drowsiness. This drug is a nonantibiotic sulfonamide that has low-level cross-reactivity with sulfa antibiotics; as a result, severe reactions are rare. Dexamethasone (8 mg/d in divided doses) is also effective. A large-scale, randomized, double-blind, placebo-controlled trial in partially acclimatized trekkers clearly showed that *Ginkgo biloba* is ineffective in the prevention of AMS. In randomized studies, ibuprofen (600 mg three times daily) has been shown to be beneficial in the prevention of AMS. Recently, acetaminophen (1 g three times daily) was as effective as ibuprofen at the above dosage in a randomized, double-blind study, which did not have a placebo arm. However, more definitive studies and (for ibuprofen) a proper gastrointestinal bleeding risk assessment need to be conducted before these drugs can be routinely recommended for AMS prevention. Many drugs, including spironolactone, medroxyprogesterone, magnesium, calcium channel blockers, and antacids, confer no benefit in the prevention of AMS. Starkly conflicting results from a number of trials of inhaled budesonide for the prevention of AMS have recently been published, but, in all likelihood, the drug is ineffective. Similarly, no efficacy studies are available for coca leaves (a weak form of cocaine), which are offered to high-altitude travelers in the Andes, or for *soroche* pills, which contain aspirin, caffeine, and acetaminophen and are sold over the counter in Bolivia and Peru. Finally, a word of caution applies in the pharmacologic prevention of altitude illness. A fast-growing population of climbers in pursuit of a summit are injudiciously using prophylactic drugs such as glucocorticoids in an attempt to improve their performance; the outcome can be tragic because of potentially severe side effects of these drugs, especially if taken for a long duration.

For the treatment of mild AMS, rest alone with analgesic use may be adequate. Descent and the use of acetazolamide and (if available) oxygen are sufficient to treat most cases of moderate AMS. Even a minor descent (400–500 m) may be adequate for symptom relief. For moderate AMS or early HACE, dexamethasone (4 mg orally or parenterally) is highly effective. For HACE, immediate descent is mandatory. When descent is not possible because of poor weather conditions or darkness, a simulation of descent in a portable hyperbaric chamber **(Fig. 462-2)** can be very effective. Pressurization in the bag for 1–2 h often leads to spectacular improvement and, like dexamethasone administration, "buys time." Thus, in certain high-altitude locations (e.g., remote pilgrimage sites), the decision to bring along the lightweight hyperbaric chamber may prove lifesaving. Like nifedipine, phosphodiesterase-5 inhibitors have no role in the treatment of AMS or HACE. Finally, short-term oxygen inhalation using small cannisters of oxygen or by visiting oxygen bars is unhelpful in the prevention of AMS.

FIGURE 462-2 A hyperbaric bag. The cylindrical, portable (<7 kg) nylon bag has a one-way valve to prevent carbon dioxide buildup. A patient with severe acute mountain sickness (AMS), high-altitude cerebral edema (HACE), or high-altitude pulmonary edema (HAPE) is zipped inside the bag, which is continuously inflated with a foot pedal. The increased barometric pressure (2 psi) inside the bag simulates descent; for example, at 4250 m, the equivalent "elevation" inside the bag is ~2100 m. No supplemental oxygen is required.

HIGH-ALTITUDE PULMONARY EDEMA

Risk Factors and Manifestations Unlike HACE (a neurologic disorder), HAPE is primarily a pulmonary problem and therefore is not necessarily preceded by AMS. HAPE develops within 2–4 days after arrival at high altitude; it rarely occurs after >4 or 5 days at the same altitude, probably because of remodeling and adaptation that render the pulmonary vasculature less susceptible to the effects of hypoxia. A rapid rate of ascent, a history of HAPE, respiratory tract infections, and cold environmental temperatures are risk factors. Men are more susceptible than women. People with abnormalities of the cardiopulmonary circulation leading to pulmonary hypertension—e.g., mitral stenosis, primary pulmonary hypertension, and unilateral absence of the pulmonary artery—may be at increased risk of HAPE, even at moderate altitudes. Although patent foramen ovale, a common condition, is four times more common among HAPE-susceptible individuals than in the general population, there is no compelling evidence to suggest causal effect. Echocardiography is recommended when HAPE develops at relatively low altitudes (<3000 m) and whenever cardiopulmonary abnormalities predisposing to HAPE are suspected. The differential diagnosis of HAPE includes anxiety attack, pneumonia, pneumothorax, and pulmonary embolism.

The initial manifestation of HAPE may be a reduction in exercise tolerance greater than that expected at the given altitude. Although a dry, persistent cough may presage HAPE and may be followed by the production of blood-tinged sputum, cough in the mountains is almost universal and the mechanism is poorly understood. Tachypnea and tachycardia, even at rest, are important markers as illness progresses. Crackles may be heard on auscultation but are not diagnostic. HAPE may be accompanied by signs of HACE. Patchy or localized opacities **(Fig. 462-3)** or streaky interstitial edema may be noted on chest radiography. In the past, HAPE was mistaken for pneumonia due to the cold or for heart failure due to hypoxia and exertion. Kerley B lines or a bat-wing appearance are not seen on radiography. Electrocardiography may reveal right ventricular strain or even hypertrophy. Hypoxemia and respiratory alkalosis are consistently present unless the patient is taking acetazolamide, in which case metabolic acidosis may supervene. Assessment of arterial blood gases is not necessary in the evaluation of HAPE; an oxygen saturation reading with a pulse oximeter is generally adequate. The existence of a subclinical form of HAPE has been suggested by an increased alveolar-arterial oxygen gradient in Everest climbers near the summit, but hard evidence correlating this abnormality with the development of clinically relevant HAPE is

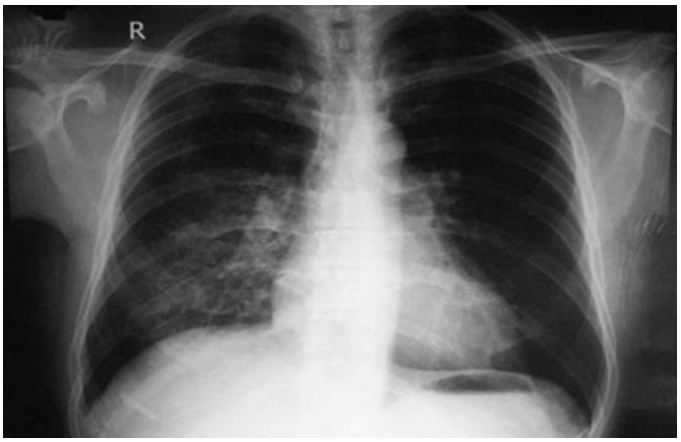

FIGURE 462-3 Chest radiograph of a patient with high-altitude pulmonary edema shows opacity in the right middle and lower zones simulating pneumonic consolidation. The opacity cleared almost completely in 2 days with descent and supplemental oxygen.

lacking. Comet-tail scoring—an ultrasound technique initially validated in cardiogenic pulmonary edema—has been used for evaluation of extravascular lung water at high altitude and has proven to be useful in detecting HAPE (clinical or subclinical) and even in ascertaining whether the presence of extravascular lung water is a harbinger of HAPE in patients with AMS.

Pathophysiology HAPE is a noncardiogenic pulmonary edema with normal pulmonary artery wedge pressure. It is characterized by patchy pulmonary hypoxic vasoconstriction that leads to overperfusion in some areas. This abnormality leads in turn to increased pulmonary capillary pressure (>18 mmHg) and capillary "stress" failure. The exact mechanism for this hypoxic vasoconstriction is unknown. Endothelial dysfunction due to hypoxia may play a role by impairing the release of nitric oxide, an endothelium-derived vasodilator. At high altitude, HAPE-prone persons have reduced levels of exhaled nitric oxide. The effectiveness of phosphodiesterase-5 inhibitors in alleviating altitude-induced pulmonary hypertension, decreased exercise tolerance, and hypoxemia supports the role of nitric oxide in the pathogenesis of HAPE. One study demonstrated that prophylactic use of tadalafil, a phosphodiesterase-5 inhibitor, decreases the risk of HAPE by 65%. In contrast, the endothelium also synthesizes endothelin-1, a potent vasoconstrictor whose concentrations are higher than average in HAPE-prone mountaineers.

Exercise and cold lead to increased pulmonary intravascular pressure and may predispose to HAPE. In addition, hypoxia-triggered increases in sympathetic drive may lead to pulmonary venoconstriction and extravasation into the alveoli from the pulmonary capillaries. Consistent with this concept, phentolamine, which elicits α-adrenergic blockade, improves hemodynamics and oxygenation in HAPE more than do other vasodilators. The study of tadalafil cited above also investigated dexamethasone in the prevention of HAPE. Surprisingly, dexamethasone reduced the incidence of HAPE by 78%—a greater decrease than with tadalafil. Besides possibly increasing the availability of endothelial nitric oxide, dexamethasone may have altered the excessive sympathetic activity associated with HAPE: the heart rate of participants in the dexamethasone arm of the study was significantly lowered. Finally, people susceptible to HAPE also display enhanced sympathetic activity during short-term hypoxic breathing at low altitudes.

Because many patients with HAPE have fever, peripheral leukocytosis, and an increased erythrocyte sedimentation rate, inflammation has been considered an etiologic factor in HAPE. However, strong evidence suggests that inflammation in HAPE is an epiphenomenon rather than the primary cause. Nevertheless, inflammatory processes (e.g., those elicited by viral respiratory tract infections) do predispose persons to HAPE—even those who are constitutionally resistant to its development.

Another proposed mechanism for HAPE is impaired transepithelial clearance of sodium and water from the alveoli. β-Adrenergic agonists upregulate the clearance of alveolar fluid in animal models. In a single double-blind, randomized, placebo-controlled study of HAPE-susceptible mountaineers, prophylactic inhalation of the β-adrenergic agonist salmeterol reduced the incidence of HAPE by 50%. However, the dosage of salmeterol (125 μg twice daily) used was very high, which could result in excessive tachycardia and tremors. Other effects of β agonists may also contribute to the prevention of HAPE, and these findings are in keeping with the concept that alveolar fluid clearance may play a pathogenic role in this illness.

Prevention and Treatment (Table 462-1) Allowing sufficient time for acclimatization by ascending gradually (as discussed above for AMS and HACE) is the best way to prevent HAPE. Sustained-release nifedipine (30 mg), given twice daily, prevents HAPE in people who must ascend rapidly or who have a history of HAPE. Other drugs for the prevention of HAPE are listed in Table 462-1 (footnote e). Although dexamethasone is listed for prevention, its adverse effect profile requires close monitoring. Acetazolamide has been shown to blunt hypoxic pulmonary vasoconstriction in animal models, and this observation warrants further study in HAPE prevention. However, one large study failed to show a decrease in pulmonary vasoconstriction in partially acclimatized individuals given acetazolamide. Inhaled salmeterol is not recommended as clinical experience with this drug is limited at high altitude. Finally, potent diuretics like furosemide should be avoided in the treatment of HAPE. Early recognition is paramount in the treatment of HAPE, especially when it is not preceded by the AMS symptoms of headache and nausea. Fatigue and dyspnea at rest may be the only initial manifestations. Descent and the use of supplementary oxygen (aimed at bringing oxygen saturation to >90%) are the most effective therapeutic interventions. Exertion should be kept to a minimum, and the patient should be kept warm. Hyperbaric therapy (Fig. 462-2) in a portable altitude chamber may be lifesaving, especially if descent is not possible and oxygen is not available. Oral sustained-release nifedipine (30 mg twice daily) can be used as adjunctive therapy. No studies have investigated phosphodiesterase-5 inhibitors in the treatment of HAPE, but reports have described their use in clinical practice. The mainstays of treatment remain descent and (if available) oxygen.

In AMS, if symptoms abate (with or without acetazolamide), the patient may reascend gradually to a higher altitude. Unlike that in acute respiratory distress syndrome (another noncardiogenic pulmonary edema), the architecture of the lung in HAPE is usually well preserved, with rapid reversibility of abnormalities (Fig. 462-3). This fact has allowed some people with HAPE to reascend slowly after a few days of descent and rest. In HACE, reascent after a few days may not be advisable during the same trip.

OTHER HIGH-ALTITUDE PROBLEMS

Sleep Impairment The mechanisms underlying sleep problems, which are among the most common adverse reactions to high altitude, include increased periodic breathing; changes in sleep architecture, with increased time in lighter sleep stages; and changes in rapid eye movement sleep. Sojourners should be reassured that sleep quality improves with acclimatization. In cases where drugs do need to be used, acetazolamide (125 mg before bedtime) is especially useful because this agent decreases hypoxemic episodes and alleviates sleeping disruptions caused by excessive periodic breathing. Whether combining acetazolamide with temazepam or zolpidem is more effective than administering acetazolamide alone is unknown. In combinations, the doses of temazepam and zolpidem should not be increased by >10 mg at high altitudes. Limited evidence suggests that diazepam causes hypoventilation at high altitudes and therefore is contraindicated. For trekkers with obstructive sleep apnea who are using a continuous positive airway pressure (CPAP) machine, the addition of acetazolamide, which will decrease centrally mediated sleep apnea, may be helpful. There is evidence to show that obstructive sleep apnea at high altitude may decrease and "convert" to central sleep apnea.

Gastrointestinal Issues High-altitude exposure may be associated with increased gastric and duodenal bleeding, but further studies are required to determine whether there is a causal effect. Because of decreased atmospheric pressure and consequent intestinal gas expansion at high altitudes, many sojourners experience abdominal bloating and distension as well as excessive flatus expulsion. In the absence of diarrhea, these phenomena are normal, if sometimes uncomfortable. Accompanying diarrhea, however, may indicate the involvement of bacteria or *Giardia* parasites, which are common at many high-altitude locations in the developing world. Prompt treatment with fluids and empirical antibiotics may be required to combat dehydration in the mountains. Hemorrhoids are common on high-altitude treks; treatment includes hot soaks, application of hydrocortisone ointment, and measures to avoid constipation.

High-Altitude Cough High-altitude cough can be debilitating and is sometimes severe enough to cause rib fracture, especially at >5000 m. The etiology of this common problem is probably multifactorial. Although high-altitude cough has been attributed to inspiration of cold dry air, this explanation appears not to be sufficient by itself; in long-duration studies in hypobaric chambers, cough has occurred

despite controlled temperature and humidity. The implication is that hypoxia also plays a role. Exercise can precipitate cough at high altitudes, possibly because of water loss from the respiratory tract. In general, infection does not seem to be a common etiology. Many trekkers find it useful to wear a balaclava to trap some moisture and heat. In most situations, cough resolves upon descent.

High-Altitude Neurologic Events Unrelated to "Altitude Illness" Transient ischemic attacks (TIAs) and strokes have been well described in high-altitude sojourners outside the setting of altitude sickness. However, these descriptions are not based on cause (hypoxia) and effect. In general, symptoms of AMS present gradually, whereas many of these neurologic events happen suddenly. The population that suffers strokes and TIAs at sea level is generally an older age group with other risk factors, whereas those so afflicted at high altitudes are generally younger and probably have fewer risk factors for atherosclerotic vascular disease. Other mechanisms (e.g., migraine, vasospasm, focal edema, hypocapneic vasoconstriction, hypoxia in the watershed zones of minimal cerebral blood flow, or cardiac right-to-left shunt) may be operative in TIAs and strokes at high altitude.

Subarachnoid hemorrhage, transient global amnesia, delirium, and cranial nerve palsies (e.g., lateral rectus palsy) occurring at high altitudes but outside the setting of altitude sickness have been well described. Syncope is common at moderately high altitudes, generally occurs shortly after ascent, usually resolves without descent, and appears to be a vasovagal event related to hypoxemia. Seizures occur rarely with HACE, but hypoxemia and hypocapnia, which are prevalent at high altitudes, are well-known triggers that may contribute to new or breakthrough seizures in predisposed individuals. Nevertheless, the consensus among experts is that sojourners with well-controlled seizure disorders can ascend to high altitudes.

Finally, persons with hypercoagulable conditions (e.g., antiphospholipid syndrome, protein C deficiency) who are asymptomatic at sea level may experience cerebral venous thrombosis (possibly due to enhanced blood viscosity triggered by polycythemia and dehydration) at high altitudes. Proper history taking, examination, and prompt investigations where possible will help define these conditions as entities separate from altitude sickness. Administration of oxygen (where available) and prompt descent are the cornerstones of treatment of most of these neurologic conditions.

Ocular Problems Ocular issues are common in sojourners to high altitudes. Hypoxemia induced by altitude leads to increased retinal blood flow, which can be visible as engorged retinal veins on ophthalmoscopic examination. Both high flow and hypoxemic vascular damage causing permeability have been implicated in a breakdown of the blood-retina barrier and the formation of retinal hemorrhages. Blot, dot, flame, and white-centered hemorrhages can be observed. These hemorrhages usually resolve spontaneously with descent, with only mild symptoms and no lasting visual damage in most healthy eyes. The exception is hemorrhage in the macular area. Macular hemorrhages can cause devastating initial visual loss, particularly if bilateral, and have been reported to cause permanently decreased vision in a few cases.

Stroke syndromes such as retinal vein occlusion, retinal artery occlusion, ischemic optic neuropathy, and cortical visual loss have all been reported. With unilateral vision loss, it is always important to check for a relative afferent pupillary defect. Increased hematocrit combined with dehydration may contribute to these maladies. Glaucomatous optic nerve damage may progress with hypoxemia of altitude. Acetazolamide is helpful both in combating the respiratory alkalosis that comes with increased ventilation at high altitude and in lowering the interocular pressure; its use should be considered in patients with stable controlled glaucoma. Macular degeneration and diabetic eye disease are not directly exacerbated by ascent to high altitude. Dry eye and solar damage to the cornea, known as "snow blindness," are common. Wearing of high-quality UV-blocking sunglasses, even on cloudy days, and attention to protecting and supplementing the tear film with artificial tear drops can greatly improve comfort and vision. Although modern refractive surgeries, such as photorefractive keratectomy (PRK) and laser in situ keratomileusis (LASIK), are stable at high altitude, patients who have undergone radial keratotomy should be cautioned that hypoxemia to the cornea can lead to swelling that shifts the refraction during ascent.

Psychological/Psychiatric Problems Delirium characterized by a sudden change in mental status, a short attention span, disorganized thinking, and an agitated state during the period of confusion has been well described in mountain climbers and trekkers without a prior history. In addition, anxiety attacks, often triggered at night by excessive periodic breathing, are well documented. The contribution of hypoxia to these conditions is unknown. Expedition medical kits need to include antipsychotic injectable drugs to control psychosis in patients in remote high-altitude locations.

PREEXISTING MEDICAL ISSUES

Because travel to high altitudes is increasingly popular, common conditions such as hypertension, coronary artery disease, and diabetes are more frequently encountered among high-altitude sojourners. This situation is of particular concern for the millions of elderly pilgrims with medical problems who visit high-altitude sacred areas (e.g., in the Himalayas) each year. In recent years, high-altitude travel has attracted intrepid trekkers who are taking immunosuppressive medications (e.g., kidney transplant recipients or patients undergoing chemotherapy). Recommended vaccinations and other precautions (e.g., hand washing) may be especially important for this group. Although most of these medical conditions do not appear to influence susceptibility to altitude illness, they may be exacerbated by ascent to altitude, exertion in cold conditions, and hypoxemia. Advice regarding the advisability of high-altitude travel and the impact of high-altitude hypoxia on these preexisting conditions is becoming increasingly relevant, but there are no evidence-based guidelines. In addition, recommendations made for relatively low altitudes (~3000 m) may not hold true for higher altitudes (>4000 m), where hypoxic stress is greater. Personal risks and benefits must be clearly thought through before ascent.

Hypertension At high altitudes, enhanced sympathetic activity may lead to a transient rise in blood pressure. Occasionally, nonhypertensive, healthy, asymptomatic trekkers have pathologically high blood pressure at high altitude that rapidly normalizes without medicines on descent. Sojourners should continue to take their antihypertensive medications at high altitudes. Importantly, hypertensive patients are not more likely than others to develop altitude illness. Because the probable mechanism of high-altitude hypertension is α-adrenergic activity, anti-α-adrenergic drugs such as prazosin have been suggested for symptomatic patients and those with labile hypertension. It is best to start taking the drug several weeks before the trip and to carry a sphygmomanometer if a trekker has labile hypertension. Sustained-release nifedipine may also be useful. A recent observational cohort study of 672 hypertensive and nonhypertensive trekkers in the Himalayas showed that most travelers, including those with well-controlled hypertension, can be reassured that their blood pressure will remain relatively stable at high altitude. Although blood pressure may be extremely elevated at high altitude in normotensive and hypertensive people, it is unlikely to cause symptoms.

Coronary Artery Disease Myocardial oxygen demand and maximal heart rate are reduced at high altitudes because the VO_2 max (maximal oxygen consumption) decreases with increasing altitude. This effect may explain why signs of cardiac ischemia or dysfunction usually are not seen in healthy persons at high altitudes. Asymptomatic, fit individuals with no risk factors need not undergo any tests for coronary artery disease before ascent. For persons with ischemic heart disease, previous myocardial infarction, angioplasty, and/or bypass surgery, an exercise treadmill test is indicated. A strongly positive treadmill test is a contraindication for high-altitude trips. Patients with poorly controlled arrhythmias should avoid high-altitude travel, but patients with arrhythmias that are well controlled with antiarrhythmic medications do not seem to be at increased risk. Sudden cardiac deaths

are not noted with a greater frequency in the Alps than at lower altitudes; although sudden cardiac deaths are encountered every trekking season in the higher Himalayan range, accurate documentation is lacking.

Cerebrovascular Disease Patients with TIAs should avoid travel to high altitude for at least 3 months. Patients with known cerebral aneurysm should also avoid high-altitude travel because of possible rupture of the aneurysm due to increased cerebral blood flow at high altitude.

Migraine Trekkers with a history of migraine may have an increased likelihood of suffering from AMS and may also be predisposed to headaches including altered character of their migraine presenting with focal neurologic deficits. Oxygen inhalation may reduce AMS-triggered headache, whereas a migraine headache usually persists even after 10–15 min of oxygen inhalation.

Asthma Although cold air and exercise may provoke acute bronchoconstriction, asthmatic patients usually have fewer problems at high than at low altitudes, possibly because of decreased allergen levels and increased circulating catecholamine levels. Nevertheless, asthmatic individuals should carry all their medications, including oral glucocorticoids, with proper instructions for use in case of an exacerbation. Severely asthmatic persons should be cautioned against ascending to high altitudes.

Pregnancy In general, low-risk pregnant women ascending to 3000 m are not at special risk except for the relative unavailability of medical care in many high-altitude locations, especially in developing countries. Despite the lack of firm data on this point, venturing higher than 3000 m to altitudes at which oxygen saturation drops steeply seems unadvisable for pregnant women.

Obesity Although living at a high altitude has been suggested as a means of controlling obesity, obesity has also been reported to be a risk factor for AMS, probably because nocturnal hypoxemia is more pronounced in obese individuals. Hypoxemia may also lead to greater pulmonary hypertension, thus possibly predisposing the trekker to HAPE.

Sickle Cell Disease High altitude is one of the rare environmental exposures that occasionally provokes a crisis in persons with sickle cell anemia. Even when traversing mountain passes as low as 2500 m, people with sickle cell anemia have been known to have a vaso-occlusive crisis. Patients with known sickle cell anemia who need to travel to high altitudes should use supplemental oxygen and travel with caution. Thalassemia has not been known to cause problems at high altitude.

Diabetes Mellitus Well-controlled diabetes is not a contraindication for travel to high altitude. Most of the high-altitude diabetes advice is based on patients with type 1 diabetes and not type 2 diabetic patients with comorbidities. An eye examination before travel may be useful. Insulin pumps are increasingly used, but bubble formation in the system may need to be closely monitored. Diabetic patients need to carry a reliable glucometer. Ready access to sweets is also essential. It is important for companions of diabetic trekkers to be fully aware of potential problems like hypoglycemia. Dexamethasone, as far as possible, should be avoided in the prevention or treatment of altitude illness in a diabetic patient.

Chronic Lung Disease Depending on disease severity and access to medical care, preexisting lung disease may not always preclude high-altitude travel. A proper pretravel evaluation must be conducted. Supplemental oxygen may be required if the predicted PaO_2 for the altitude is <50–55 mmHg. Preexisting pulmonary hypertension may also need to be assessed in these patients. If the result is positive, patients should be discouraged from ascending to high altitudes; if such travel is necessary, treatment with sustained-release nifedipine (20 mg twice a day) should be considered. Small-scale studies have revealed that when patients with bullous disease reach ~5000 m, bullous expansion and pneumothorax are not noted. Compared with information on chronic obstructive pulmonary disease, fewer data exist about the safety of travel to high altitude for people with pulmonary fibrosis, but acute exacerbation of pulmonary fibrosis has been seen at high altitude. A handheld pulse oximeter can be useful to check for oxygen saturation.

Chronic Kidney Disease Patients with chronic kidney disease can tolerate short-term stays at high altitudes, but theoretical concern persists about progression to end-stage renal disease. Acetazolamide, the drug most commonly used for altitude sickness, should be avoided by anyone with preexisting metabolic acidosis, which can be exacerbated by this drug. In addition, the acetazolamide dosage should be adjusted when the glomerular filtration rate falls to <50 mL/min, and the drug should not be used at all if this value falls to <10 mL/min.

Cirrhosis Of patients with cirrhosis, 16% may have portopulmonary arterial hypertension, and 32% may have hepatopulmonary syndrome; these conditions may be detrimental at high altitude as they may cause exaggerated hypoxemia. Thus, screening for these problems is important in cirrhotic patients planning a high-altitude trip. In addition, acetazolamide may be inadvisable in these patients as the drug may increase the risk of hepatic encephalopathy.

Dental Problems Air resulting from decay in the root system could expand on ascent and lead to increasing pain. A good dental checkup before a trekking or climbing trip may be prudent.

CHRONIC MOUNTAIN SICKNESS AND HIGH-ALTITUDE PULMONARY HYPERTENSION IN HIGHLANDERS

The largest populations of highlanders live in the South American Andes, the Tibetan Plateau, and parts of Ethiopia. Chronic mountain sickness (*Monge's disease*) is a disease in highlanders that is characterized by excessive erythrocytosis with moderate to severe pulmonary hypertension leading to cor pulmonale. This condition was originally described in South America and has also been documented in Colorado and in the Han Chinese population in Tibet; it is much less common in Tibetans or in Ethiopian highlanders. Migration to a low altitude results in the resolution of chronic mountain illness. Venesection and acetazolamide are helpful.

High-altitude pulmonary hypertension is also a subacute disease of long-term high-altitude residents. Unlike Monge's disease, this syndrome is characterized primarily by pulmonary hypertension (not erythrocytosis) leading to heart failure. Indian soldiers living at extreme altitudes for prolonged periods and Han Chinese infants born in Tibet have presented with the adult and infantile forms, respectively. High-altitude pulmonary hypertension bears a striking pathophysiologic resemblance to brisket disease in cattle. Descent to a lower altitude is curative.

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463 Hyperbaric and Diving Medicine

Michael H. Bennett, Simon J. Mitchell

WHAT IS HYPERBARIC AND DIVING MEDICINE?

Hyperbaric medicine is the treatment of health disorders using whole-body exposure to pressures >101.3 kPa (1 atmosphere or 760 mmHg). In practice, this almost always means the administration of *hyperbaric oxygen therapy* (HBO_2T). The Undersea and Hyperbaric Medical Society (UHMS) defines HBO_2T as: "an intervention in which an individual breathes near 100% oxygen intermittently while inside a hyperbaric chamber that is pressurized to greater than sea level pressure (1 atmosphere absolute, or ATA). For clinical purposes, the pressure must equal or exceed 1.4 ATA." The chamber is an airtight vessel variously called a hyperbaric chamber, recompression chamber, or decompression chamber, depending on the clinical and historical context. Such chambers may be capable of compressing a single patient (a monoplace chamber) or multiple patients and attendants as required (a multiplace chamber) **(Figs. 463-1 and 463-2)**. Historically, these compression chambers were first used for the treatment of divers and compressed air workers suffering decompression sickness (DCS; "the bends"). Although the prevention and treatment of disorders arising after decompression in diving, aviation, and space flight have developed into a specialized field of their own, they remain closely linked to the broader practice of hyperbaric medicine.

Despite an increased understanding of mechanisms and an improving evidence basis, hyperbaric medicine has struggled to achieve widespread recognition as a "legitimate" therapeutic measure. There are several contributing factors, but high among them are a poor grounding in general oxygen physiology and oxygen therapy at medical schools and a continuing tradition of charlatans advocating hyperbaric therapy (often using air) as a panacea. Funding for both basic and clinical research has been difficult in an environment where the pharmacologic agent under study is abundant, cheap, and unpatentable. There are signs of an improved appreciation of the potential importance of HBO_2T with significant National Institutes of Health (NIH) funding for mechanisms research, from the U.S. military for clinical investigation, and as evidenced by the recent appreciation of HBO_2T as a potentially useful tool for improving oxygenation in severe COVID-19 (see "Further Readings").

MECHANISMS OF HYPERBARIC OXYGEN

Increased hydrostatic pressure will reduce the volume of any bubbles present within the body (see "Diving Medicine"), and this is partly responsible for the success of prompt recompression in DCS and arterial gas embolism. Supplemental oxygen breathing has a dose-dependent effect on oxygen transport, ranging from improvement in hemoglobin oxygen saturation when a few liters per minute are delivered by simple mask at 101.3 kPa (1 ATA) to raising the dissolved plasma oxygen sufficiently to sustain life without the need for hemoglobin at all when 100% oxygen is breathed at 303.9 kPa (3 ATA). Most HBO_2T regimens involve oxygen breathing at between 202.6 and 283.6 kPa (2 and 2.8 ATA), and the resultant increase in arterial oxygen tensions to >133.3 kPa (1000 mmHg) has widespread physiologic and pharmacologic consequences **(Fig. 463-3)**.

FIGURE 463-1 A monoplace chamber. *(Prince of Wales Hospital, Sydney.)*

FIGURE 463-2 A chamber designed to treat multiple patients. *(Karolinska University Hospital.)*

One direct consequence of such high intravascular tension is to increase greatly the effective capillary-tissue diffusion distance for oxygen such that oxygen-dependent cellular processes can resume in hypoxic tissues. Important as this may be, the mechanism of action is not limited to this restoration of oxygenation in hypoxic tissue. Indeed, there are pharmacologic effects that are profound and long-lasting. Although removal from the hyperbaric chamber results in a rapid return of poorly vascularized tissues to their hypoxic state, even a single dose of HBO_2T produces changes in fibroblast, leukocyte and angiogenic functions, and antioxidant defenses that persist many hours after oxygen tensions are returned to pretreatment levels.

It is widely accepted that oxygen in high doses produces adverse effects due to the production of reactive oxygen species (ROS) such as superoxide (O_2^-) and hydrogen peroxide (H_2O_2). It has become increasingly clear over the past decade that both ROS and reactive nitrogen species (RNS) such as nitric oxide (NO) participate in diverse intracellular signaling pathways involved in the production of a range of cytokines, growth factors, and other inflammatory and repair modulators. Such mechanisms are complex and at times apparently paradoxical. For example, when used to treat chronic hypoxic wounds, HBO_2T has been shown to enhance the clearance of cellular debris and bacteria by providing the substrate for macrophage phagocytosis; stimulate growth factor synthesis by increased production and stabilization of hypoxia-inducible factor 1 (HIF-1); inhibit leukocyte activation and adherence to damaged endothelium; and mobilize CD34+ pluripotent vasculogenic progenitor cells from the bone marrow. The interactions between these mechanisms remain a very active field of investigation. One exciting development is the concept of *hyperoxic preconditioning* in which a short exposure to HBO_2 can induce tissue protection against future hypoxic/ischemic insult, most likely through an inhibition of mitochondrial permeability transition pore (MPTP) opening and the release of cytochrome c. By targeting these mechanisms of cell death during reperfusion events, HBO_2 has potential applications in a variety of settings including organ transplantation. One randomized clinical trial suggested that HBO_2T prior to coronary artery bypass grafting reduces biochemical markers of ischemic stress and improves neurocognitive outcomes.

ADVERSE EFFECTS OF THERAPY

HBO_2T is generally well tolerated and safe in clinical practice. About 17% of patients experience an adverse event at some time during their treatment course, and most are mild and self-limiting. Adverse effects

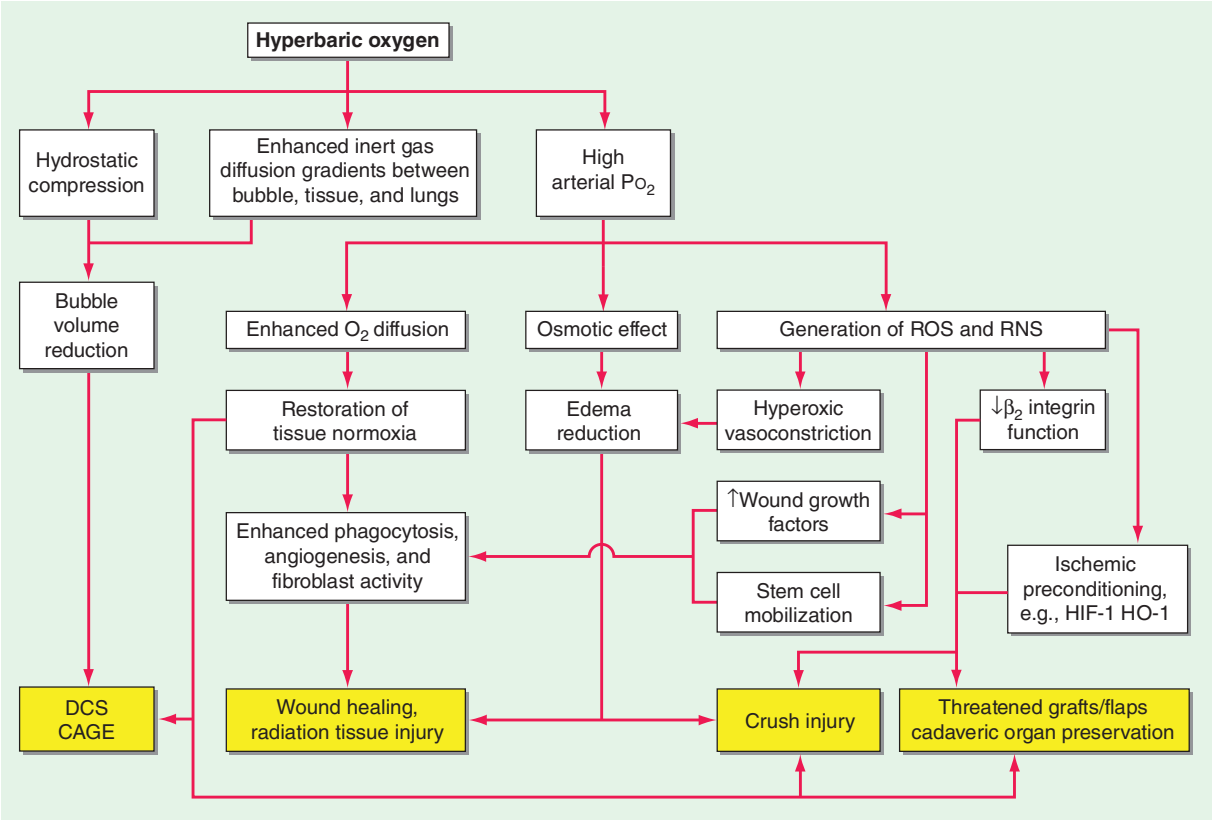

FIGURE 463-3 Mechanisms of action of hyperbaric oxygen. There are many consequences of compression and oxygen breathing. The cell-signaling effects of hyperbaric oxygen therapy (HBO_2T) are the least understood but potentially most important. Examples of indications for use are shown in the shaded boxes. CAGE, cerebral arterial gas embolism; DCS, decompression sickness; HIF-1, hypoxia-inducible factor-1; HO-1, hemoxygenase 1; RNS, reactive nitrogen species; ROS, reactive oxygen species.

are associated with both alterations in pressure (barotrauma) and the administration of oxygen.

BAROTRAUMA

Barotrauma occurs when any noncompliant gas-filled space within the body does not equalize with environmental pressure during compression or decompression. About 10% of patients complain of some difficulty equalizing middle-ear pressure early in compression, and although most of these problems are minor and can be overcome with training, 2–5% of conscious patients require middle-ear ventilation tubes or formal grommets across the tympanic membrane. Unconscious patients cannot equalize and should have middle-ear ventilation tubes placed prior to compression if possible. Other less common sites for barotrauma of compression include the respiratory sinuses and dental caries. The lungs are potentially vulnerable to barotrauma of decompression as described below in the section on diving medicine, but the decompression following HBO_2T is so slow that pulmonary gas trapping is extremely rare in the absence of an undrained pneumothorax or lesions such as bullae.

OXYGEN TOXICITY

The practical limit to the dose of oxygen, either in a single treatment session or in a series of daily sessions, is oxygen toxicity. The most common acute manifestation is a seizure, often preceded by anxiety and agitation, during which time a switch from oxygen to air breathing may avoid the convulsion. Hyperoxic seizures are typically generalized tonic-clonic seizures followed by a variable postictal period. The cause is an overwhelming of the antioxidant defense systems within the brain. Although clearly dose-dependent, onset is very variable both between individuals and within the same individual on different days. In routine clinical hyperbaric practice, the incidence is ~1:1500 to 1:3000 compressions.

Chronic oxygen poisoning most commonly manifests as myopic shift. This is due to alterations in the refractive index of the lens following oxidative damage that reduces the solubility of lenticular proteins in a process similar to that associated with senescent cataract formation. Up to 75% of patients show deterioration in visual acuity after a course of 30 treatments at 202.6 kPa (2 ATA). Although most return to pretreatment values 6–12 weeks after cessation of treatment, a small proportion do not recover. A more rapid maturation of preexisting cataracts has occasionally been associated with HBO_2T. Although a theoretical problem, the development of pulmonary oxygen toxicity over time does not seem to be problematic in practice—probably due to the intermittent nature of the exposure.

CONTRAINDICATIONS TO HYPERBARIC OXYGEN

There are few absolute contraindications to HBO_2T. The most commonly encountered is an untreated pneumothorax. A pneumothorax may expand rapidly on decompression and come under tension. Prior to any compression, patients with a pneumothorax should have a patent chest drain in place. The presence of other obvious risk factors for pulmonary gas trapping such as bullae should trigger a very cautious analysis of the risks of treatment versus benefit. Prior bleomycin treatment deserves special mention because of its association with a partially dose-dependent pneumonitis in ~20% of people. These individuals appear to be at particular risk for rapid deterioration of ventilatory function following exposure to high oxygen tensions. The relationship between distant bleomycin exposure and subsequent risk of pulmonary oxygen toxicity is uncertain; however, late pulmonary fibrosis is a potential complication of bleomycin, and any patient with a history of receiving this drug should be carefully counseled prior to exposure to HBO_2T. For those recently exposed to doses >300,000 IU (200 mg) and whose course was complicated by a respiratory reaction to bleomycin, compression should be avoided except in a life-threatening situation.

INDICATIONS FOR HYPERBARIC OXYGEN

The appropriate indications for HBO_2T are controversial and evolving. Practitioners in this area are in an unusual position. Unlike most branches of medicine, hyperbaric physicians do not deal with a range of disorders within a defined organ system, nor are they masters of a therapy specifically designed for a single category of disorders.

TABLE 463-1 Current List of Indications for Hyperbaric Oxygen Therapy

1. Air or gas embolism (includes diving-related, iatrogenic, and accidental causes)
2. Carbon monoxide poisoning (including poisoning complicated by cyanide poisoning)
3. Clostridial myositis and myonecrosis (gas gangrene)
4. Crush injury, compartment syndrome, and acute traumatic ischemias
5. Decompression sickness
6. Arterial insufficiency including central retinal arterial occlusion and problem wounds
7. Severe anemia
8. Intracranial abscess
9. Necrotizing soft tissue infections (e.g., Fournier's gangrene)
10. Osteomyelitis (refractory to other therapy)
11. Delayed radiation injury (soft-tissue injury and bony necrosis)
12. Skin grafts and flaps (compromised)
13. Acute thermal burn injury
14. Sudden sensorineural hearing loss

Source: The Undersea and Hyperbaric Medical Society (2021).

Inevitably, the encroachment of hyperbaric physicians into other medical fields generates suspicion from specialist practitioners in those fields. At the same time, this relatively benign therapy, the prescription and delivery of which requires no medical license in most jurisdictions (including the United States), attracts both charlatans and well-motivated proselytizers who tout the benefits of oxygen for a plethora of chronic incurable diseases. This battle on two fronts has meant that mainstream hyperbaric physicians have been particularly careful to claim effectiveness only for those conditions where there is a reasonable body of supporting evidence.

In 1977, the UHMS systematically examined claims for the use of HBO_2T in >100 disorders and found sufficient evidence to support routine use in only 12. The Hyperbaric Oxygen Therapy Committee of that organization has continued to update this list periodically with an increasingly formalized system of appraisal for new indications and emerging evidence **(Table 463-1)**. Around the world, other relevant medical organizations have generally taken a similar approach. Indications vary considerably across the globe—particularly those recommended by hyperbaric medical societies in Russia and China where HBO_2T has gained much wider support than in the United States, Europe, and Australasia. Nevertheless, there are now 31 Cochrane reviews summarizing the randomized trial evidence for 27 putative indications, including attempts to examine the cost-effectiveness of HBO_2T. **Table 463-2** is a synthesis of these two approaches and lists the estimated cost of attaining health outcomes with the use of HBO_2T. Any savings associated with alternative treatment strategies avoided as a result of HBO_2T are not accounted for in these estimates (e.g., the avoidance of lower leg amputation in diabetic foot ulcers). Following are short reviews of three important indications currently accepted by the UHMS.

LATE RADIATION TISSUE INJURY

Radiotherapy is a well-established treatment for suitable malignancies. In the United States alone, ~300,000 individuals annually will become long-term survivors of cancer treated by irradiation. Serious radiation-related complications developing months or years after treatment (late radiation tissue injury [LRTI]) will significantly affect between 5 and 15% of those long-term survivors, although incidence varies widely with dose, age, and site. LRTI is most common in the head and neck, chest wall, breast, and pelvis.

Pathology and Clinical Course With time, tissues undergo a progressive deterioration characterized by a reduction in the density of small blood vessels (reduced vascularity) and the replacement of normal tissue with dense fibrous tissue (fibrosis). An alternative model of pathogenesis suggests that rather than a primary hypoxia, the principal trigger is an overexpression of inflammatory cytokines that promote fibrosis, probably through oxidative stress and mitochondrial dysfunction, and a secondary tissue hypoxia. Ultimately, and often triggered by a further physical insult such as surgery or infection, there may be insufficient oxygen to sustain normal function, and the tissue becomes necrotic (radiation necrosis). LRTI may be life-threatening and significantly reduce quality of life. Historically, the management of these injuries has been unsatisfactory. Conservative treatment is usually restricted to symptom management, whereas definitive treatment traditionally entails surgery to remove the affected part and extensive repair. Surgical intervention in an irradiated field is often disfiguring and associated with an increased incidence of delayed healing, breakdown of a surgical wound, or infection. HBO_2T may act by several mechanisms to improve this situation, including edema reduction, vasculogenesis, and enhancement of macrophage activity (Fig. 463-3). The intermittent application of HBO_2 is the only intervention shown to increase the microvascular density in irradiated tissue.

Clinical Evidence The typical course of HBO_2T consists of 30 once-daily compressions to 202.6–243.1 kPa (2–2.4 ATA) for 1.5–2 h each session, often bracketed around surgical intervention if required. Although HBO_2T has been used for LRTI since at least 1975, most clinical studies have been limited to small case series or individual case reports. In a review, Feldmeier and Hampson located 71 such reports involving a total of 1193 patients across eight different tissues. There were clinically significant improvements in the majority of patients, and only 7 of 71 reports indicated a generally poor response to HBO_2T. A Cochrane systematic review with meta-analysis included 14 randomized trials published since 1985 and drew the following conclusions (see Table 463-2 for numbers needed to treat): HBO_2T improves healing in radiation proctitis (relative risk [RR] of healing with HBO_2T, 1.72; 95% confidence interval [CI], 1.0–2.9) and achievement of mucosal cover of bone after hemimandibulectomy and reconstruction of the mandible (RR, 1. 3; 95% CI, 1.1–1.6); HBO_2T prevents the development of osteoradionecrosis following tooth extraction from a radiation field (RR, 1.4; 95% CI, 1.08–1.7) and reduces the risk of wound dehiscence following grafts and flaps in the head and neck (RR, 4.2; 95% CI, 1.1–16.8). Conversely, there was no evidence of benefit in established radiation brachial plexus lesions or brain injury.

SELECTED PROBLEM WOUNDS

A problem wound is any cutaneous ulceration that requires a prolonged time to heal, does not heal, or recurs. In general, wounds referred to hyperbaric facilities are those where sustained attempts to heal by other means have failed. Problem wounds are common and constitute a significant health problem. It has been estimated that 1% of the population of industrialized countries will experience a leg ulcer at some time. The global cost of chronic wound care may be as high as U.S. $25 billion per year.

Pathology and Clinical Course By definition, chronic wounds are indolent or progressive and resistant to the wide array of treatments applied. Although there are many contributing factors, most commonly, these wounds arise in association with one or more comorbidities such as diabetes, peripheral venous or arterial disease, or prolonged pressure (decubitus ulcers). First-line treatments are aimed at correction of the underlying pathology (e.g., vascular reconstruction, compression bandaging, or normalization of blood glucose level), and HBO_2T is an adjunctive therapy to good general wound care practice to maximize the chance of healing.

For most indolent wounds, hypoxia is a major contributor to failure to heal. Many guidelines to patient selection for HBO_2T include the interpretation of transcutaneous oxygen tensions around the wound while breathing air and oxygen at pressure **(Fig. 463-4)**. Wound healing is a complex and incompletely understood process. While it appears that in acute wounds healing is stimulated by the initial hypoxia, low pH, and high lactate concentrations found in freshly injured tissue, some elements of tissue repair are extremely oxygen dependent, for example, collagen elaboration and deposition by fibroblasts and bacterial killing by macrophages. In this complicated interaction between

TABLE 463-2 Selected Indications for Which There Is Promising Efficacy for the Application of Hyperbaric Oxygen Therapy

DIAGNOSIS	OUTCOME (NUMBER OF SESSIONS)	NNT AND 95% CI	ESTIMATED COST TO PRODUCE ONE EXTRA FAVORABLE OUTCOME AND 95% CI (USD)	COMMENTS AND RECOMMENDATIONS
Radiation tissue injury	**More information is required on the subset of disease severity, the affected tissue type that is most likely to benefit, and the time over which benefit may persist.**			
	Resolved proctitis (30)	3	22,392	Large ongoing multicenter trial
		2–11	14,928–82,104	
	Healed mandible (30)	4	29,184	Based on one poorly reported study
		2–8	14,592–58,368	
	Mucosal cover in ORN (30)	3	29,888	Based on one poorly reported study
		2–4	14,592–29,184	
	Bony continuity in ORN (30)	4	29,184	Based on one poorly reported study
		2–8	14,592–58,368	
	Prevention of ORN after dental extraction (30)	4	29,184	Based on a single study
		2–13	14,592–94,848	
	Prevention of dehiscence (30)	5	36,480	Based on one poorly reported study
		3–8	21,888–58,368	
Chronic wounds	**More information is required on the subset of disease severity or classification most likely to benefit, the time over which benefit may persist, and the most appropriate oxygen dose. Economic analysis is required.**			
	Diabetic ulcer healed at 1 year (30)	2	14,928	Based on one small study, more research required
		1–5	7464–37,320	
	Diabetic ulcer, major amputation avoided (30)	4	29,856	Three small studies; outcome over a longer time period required
		3–11	22,392–82,104	
ISSNHL	**No evidence of benefit >2 weeks after onset. More research is required to define the role (if any) of HBO_2T in routine therapy.**			
	Improvement of 25% in hearing loss within 2 weeks of onset (15)	5	18,240	Some improvement in hearing, but functional significance unknown
		3–20	10,944–72,960	
Acute coronary syndrome	**More information is required on the subset of disease severity and timing of therapy most likely to result in benefit. Given the potential of HBO_2T in modifying ischemia-reperfusion injury, attention should be given to the combination of HBO_2T and thrombolysis in early management and in the prevention of restenosis after stent placement.**			
	Episode of MACE (5)	4	4864	Based on a single small study; more research required
		3–10	3648–12,160	
	Incidence of significant dysrhythmia (5)	6	7296	Based on a single moderately powered study in the 1970s
		3–24	3648–29,184	
Traumatic brain injury	**Limited evidence that for acute injury HBO_2T reduces mortality but not functional morbidity. Routine use not yet justified.**			
	Mortality (15)	7	34,104	Based on four heterogeneous studies
		4–22	19,488–58,464	
Enhancement of radiotherapy	**There is some evidence that HBO_2T improves local tumor control, reduces mortality for cancers of the head and neck, and reduces the chance of local tumor recurrence in cancers of the head, neck, and uterine cervix.**			
	Head and neck cancer: 5-year mortality (12)	5	14,592	Based on trials performed in the 1970s and 1980s. There may be some confounding by radiation fractionation schedule.
		3–14	8755–40,858	
	Local recurrence 1 year (12)	5	14,592	May no longer be relevant to therapy
		4–8	11,674–23,347	
	Cancer of uterine cervix: Local recurrence at 2 years (20)	5	24,320	As above
		4–8	19,456–38,912	
Decompression illness[a]	**Reasonable evidence for reduced number of HBO_2T sessions but similar outcomes when NSAID added.**			
	Reduction of HBO_2T treatment requirement by 1	5	N/R	Single appropriately powered randomized trial
		3–18		

[a]Tenoxicam used as an adjunct to recompression on oxygen.

Abbreviations: CI, confidence interval; HBO_2T, hyperbaric oxygen therapy; ISSNHL, idiopathic sudden sensorineural hearing loss; MACE, major adverse cardiac events; NNT, number needed to treat; N/R, not remarkable; NSAID, nonsteroidal anti-inflammatory drug; ORN, osteoradionecrosis; USD, U.S. dollars.

Source: M Bennett: The evidence-basis of diving and hyperbaric medicine—a synthesis of the high level evidence with meta-analysis. *http://unsworks.unsw.edu.au/fapi/datastream/unsworks:949/SOURCE01?view=true*.

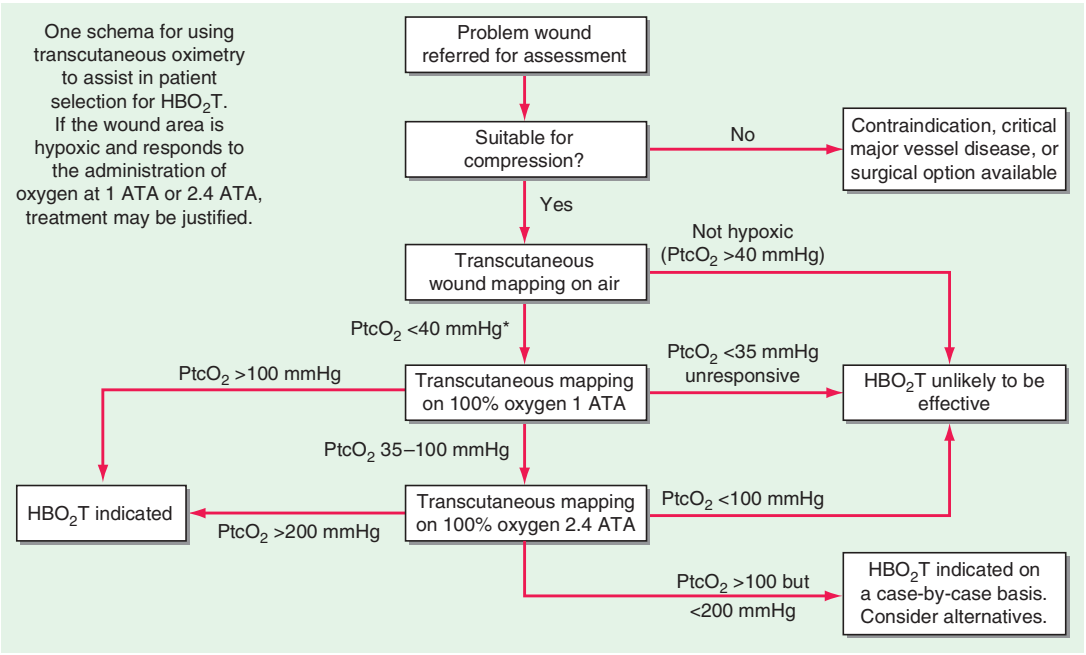

FIGURE 463-4 Determining suitability for hyperbaric oxygen therapy (HBO_2T) guided by transcutaneous oximetry around the wound bed. *In diabetic patients, <50 mmHg may be more appropriate. $PtcO_2$, transcutaneous oxygen pressure.

wound hypoxia and periwound oxygenation, successful healing relies on adequate tissue oxygenation in the area surrounding the fresh wound. Certainly, wounds that lie in hypoxic tissue beds are those that most often display poor or absent healing. Some causes of tissue hypoxia will be reversible with HBO_2T, whereas some will not (e.g., in the presence of severe large vessel disease). When tissue hypoxia can be overcome by a high driving pressure of oxygen in the arterial blood, this can be demonstrated by measuring the tissue partial pressure of oxygen using an implantable oxygen electrode or, more commonly, a modified transcutaneous Clarke electrode.

The intermittent presentation of oxygen to those hypoxic tissues facilitates a resumption of healing. These short exposures to high oxygen tensions have long-lasting effects (at least 24 h) on a wide range of healing processes (Fig. 463-3). The result is a gradual improvement in oxygen tension around the wound that reaches a plateau in experimental studies at ~20 treatments over 4 weeks. Improvements in oxygenation are associated with an eight- to ninefold increase in vascular density over both normobaric oxygen and air-breathing controls.

Clinical Evidence The typical course of HBO_2T consists of 20–30 once-daily compressions to 2–2.4 ATA for 1.5–2 h each session but is highly dependent on the clinical response. There are many case series in the literature supporting the use of HBO_2T for a wide range of problem wounds. Both retrospective and prospective cohort studies suggest that 6 months after a course of therapy, ~70% of indolent ulcers will be substantially improved or healed. Often these ulcers have been present for many months or years, suggesting the application of HBO_2T has a profound effect, either primarily or as a facilitator of other strategies. A recent Cochrane review included 12 randomized controlled trials (RCTs) and concluded that the chance of a diabetic ulcer healing improved with HBO_2T (10 trials; RR, 2.35; 95% CI, 1.19–4.62; $p = .01$). Although there was a trend to benefit with HBO_2T, there was no statistically significant difference in the rate of major amputations (RR, 0.36; 95% CI, 0.11–1.18).

CARBON MONOXIDE POISONING

Carbon monoxide (CO) is a colorless, odorless gas formed during incomplete hydrocarbon combustion. Although CO is an essential endogenous neurotransmitter linked to NO metabolism and activity, it is also a leading cause of poisoning death and, in the United States alone, results in >50,000 emergency department visits per year and ~2000 deaths. Although there are large variations from country to country, about half of nonlethal exposures are due to self-harm. Accidental poisoning is commonly associated with defective or improperly installed heaters, house fires, and industrial exposures. The motor vehicle is by far the most common source of intentional poisoning.

Pathology and Clinical Course The pathophysiology of CO exposure is incompletely understood. CO binds to hemoglobin with an affinity >200 times that of oxygen, directly reducing the oxygen-carrying capacity of blood and further promoting tissue hypoxia by shifting the oxyhemoglobin dissociation curve to the left. CO is also an anesthetic agent that inhibits evoked responses and narcotizes experimental animals in a dose-dependent manner. The associated loss of airway patency together with reduced oxygen carriage in blood may cause death from acute arterial hypoxia in severe poisoning. CO may also cause harm by other mechanisms including direct disruption of cellular oxidative processes, binding to myoglobin and hepatic cytochromes, and peroxidation of brain lipids.

The brain and heart are the most sensitive target organs due to their high blood flow, poor tolerance of hypoxia, and high oxygen requirements. Minor exposure may be asymptomatic or present with vague constitutional symptoms such as headache, lethargy, and nausea, whereas higher doses may present with poor concentration and cognition, short-term memory loss, confusion, seizures, and loss of consciousness. While carboxyhemoglobin (COHb) levels on admission do not necessarily reflect the severity or the prognosis of CO poisoning, cardiorespiratory arrest carries a very poor prognosis. Over the longer term, surviving patients commonly have neuropsychological sequelae. Motor disturbances, peripheral neuropathy, hearing loss, vestibular abnormalities, dementia, and psychosis have all been reported. Risk factors for poor outcome are age >35 years, exposure for >24 h, acidosis, and loss of consciousness.

Clinical Evidence The typical course of HBO_2T consists of two to three compressions to 2–2.8 ATA for 1.5–2 h each session. It is common for the first two compressions to be delivered within 24 h of the exposure. CO poisoning is one of the longest-standing indications for HBO_2T—based largely on the obvious connection between exposure, tissue hypoxia, and the ability of HBO_2T to rapidly overcome this hypoxia. CO is eliminated rapidly via the lungs on application of HBO_2T, with a half-life of ~21 min at 2.0 ATA versus 5.5 h breathing air and 71 min breathing oxygen at sea level. In practice, however, it seems unlikely that HBO_2T can be delivered in time to prevent either

acute hypoxic death or irreversible global cerebral hypoxic injury. If HBO_2T is beneficial in CO poisoning, it must reduce the likelihood of persisting and/or delayed neurocognitive deficit through a mechanism other than the simple reversal of arterial hypoxia due to high levels of COHb. The difficulty in accurately assessing neurocognitive deficit has been one of the primary sources of controversy surrounding the clinical evidence in this area. To date, there have been six RCTs of HBO_2T for CO poisoning, although only four have been reported in full. While a Cochrane review suggested there is insufficient evidence to confirm a beneficial effect of HBO_2T on the chance of persisting neurocognitive deficit following poisoning (34% of patients treated with oxygen at 1 atmosphere vs 29%, of those treated with HBO_2T; odds ratio [OR], 0.78; 95% CI, 0.54–1.1), this may have more to do with poor reporting and inadequate follow-up than with evidence that HBO_2T is not effective. The interpretation of the literature has much to do with how one defines neurocognitive deficit. In the most methodologically rigorous of these studies (Weaver et al.), a professionally administered battery of validated neuropsychological tests and a definition based on the deviation of individual subtest scores from the age-adjusted normal values was used; if the patient complained of memory, attention, or concentration difficulties, the required decrement was decreased. Using this approach, 6 weeks after poisoning, 46% of patients treated with normobaric oxygen alone had cognitive sequelae compared to 25% of those who received HBO_2T ($p = .007$; number needed to treat [NNT] = 5; 95% CI, 3–16). At 12 months, the difference remained significant (32 vs 18%; $p = .04$; NNT = 7; 95% CI, 4–124) despite considerable loss to follow-up.

On this basis, HBO_2T remains widely advocated for the routine treatment of patients with moderate to severe poisoning—in particular in those older than 35 years, presenting with a metabolic acidosis on arterial blood-gas analysis, exposed for lengthy periods, or with a history of unconsciousness. Conversely, many toxicologists remain unconvinced about the place of HBO_2T in this situation and call for further well-designed studies.

CURRENT CONTROVERSIES IN HYPERBARIC MEDICINE

The use of hyperbaric oxygen has been associated with controversy since it was first instituted in the 1950s. A vigorous debate has recently developed around the concept of performing sham controlled RCTs, particularly when assessing outcomes where a placebo effect could significantly influence interpretation. The most popular method employed to achieve blinding of both staff and patients is the exposure of patients in the control arm to a modest pressure while breathing air in the chamber (between 1.1 and 1.3 ATA). While this strategy is effective in blinding the exposure, critics claim this exposure to air at pressure (equivalent to breathing ~27% oxygen at 1.0 ATA) is therapeutic in a way yet to be identified. These critics use this putative therapeutic effect to explain the modest measured benefits in patients with a range of chronic neurologic conditions including cerebral palsy, autism spectrum disorders, and mild traumatic brain injury when exposed to either air at 1.1–1.3 ATA or 100% oxygen at 2.0–2.4 ATA (HBO_2T) in a number of trials. These benefits have traditionally been interpreted as the result of a participation or placebo effect, with the various authors concluding there was no evidence of a specific effect for HBO_2T in any of these conditions. The search continues for a convincing sham exposure that is universally regarded as inactive. Some workers claim this is not possible and that patient-blinded trials are therefore similarly unachievable. This impasse needs resolution, and there is some hope that the restriction of pressure exposure to short periods of modest compression at the start and end of each sham session may be convincing for both sides of the argument.

DIVING MEDICINE

INTRODUCTION

Underwater diving is both a popular recreational activity and a means of employment in a range of tasks from underwater construction to military operations. It is a complex activity with unique hazards and medical complications arising mainly as a consequence of the dramatic changes in pressure associated with both descent and ascent through the water column. For every 10.1-m increase in depth of seawater, the ambient pressure (P_{amb}) increases by 101.3 kPa (1 atmosphere) so that, for example, a diver at 20 m depth is exposed to a P_{amb} of 303.9 kPa (3 ATA), made up of 1 ATA due to atmospheric pressure and 2 ATA generated by the water column.

BREATHING EQUIPMENT

Most diving is undertaken using self-contained underwater breathing apparatus (scuba) consisting of one or more cylinders of compressed gas connected to a pressure-reducing regulator and a demand valve activated by inspiratory effort. Some divers use "rebreathers," which comprise a closed or semi-closed breathing circuit with a carbon dioxide scrubber and an oxygen addition system designed to maintain a safe inspired Po_2. Exhaled gas is recycled, and gas consumption is limited to little more than the oxygen metabolized by the diver. Rebreathers are therefore popular for deep dives where expensive helium is included in the respired mix (see below). Occupational divers frequently use "surface supply" equipment where gas, along with other utilities such as communications and power, is supplied via an "umbilical" cable from the surface.

All these systems must supply gas to the diver at the P_{amb} of the surrounding water or inspiration would be impossible against the water pressure. For most recreational diving, the respired gas is air. Pure oxygen is rarely used because there is a dose-dependent risk (where "dose" is a function of exposure time and inspired Po_2) that oxygen may provoke seizures above an inspired Po_2 of 130 kPa (1.3 ATA). The maximum acceptable inspired Po_2 in diving is often considered to be 161 kPa (1.6 ATA), which would be achieved when breathing pure oxygen at 6 m or air at 66 m. This is a conspicuously lower Po_2 than routinely used for hyperbaric therapy (see earlier), reflecting a higher risk of oxygen toxic seizures during immersion and exercise. In order to avoid dangerous oxygen exposures, very deep diving requires the use of inspired oxygen fractions lower than in air (Fo_2 0.21), and divers tailor the oxygen content of their gases to remain within recommended exposure guidelines. Deep-diving gases include helium as a substitute for some or all of the nitrogen to reduce both the narcotic effect and high gas density that result from breathing nitrogen at high pressures.

SUITABILITY FOR DIVING

The most common reason for physician consultation in relation to diving is for the evaluation of suitability for diver training or continuation of diving after a health event. Occupational diver candidates are usually compelled to see doctors with specialist training in the field, both at entry to the industry and periodically thereafter, and their medical evaluations are usually conducted according to legally mandated standards. In contrast, in most jurisdictions, prospective recreational diver candidates simply complete a self-assessment medical questionnaire prior to diver training. If there are no positive responses, the candidate proceeds directly to training, but positive responses mandate the candidate see a doctor for evaluation of the identified medical issue. Prospective divers will often present to their family medicine practitioner for this purpose. In the modern era, such consultations have evolved from a simple proscriptive exercise of excluding those with potential contraindications to an approach in which each case is considered on its own merits and an individualized evaluation of risk is made. Such evaluations require integration of diving physiology, the impact of associated medical problems, and knowledge of the specific medical condition(s) of the candidate. A detailed discussion is beyond the scope of this chapter, but several important principles are outlined below.

There are three primary questions that should be answered in relation to any medical condition reported by a prospective diver: (1) Could the condition be exacerbated by diving? (2) Could the condition make a diving medical problem more likely? (3) Could the condition prevent the diver from meeting the functional requirements of diving? As examples of positive answers to these questions (respectively): epilepsy is usually considered to imply high risk because there are epileptogenic stimuli such as high inspired oxygen pressures encountered in diving that could make a seizure (and drowning) more likely; active

asthma is considered to increase risk because it could predispose to air trapping and pulmonary barotrauma (see below); and ischemic heart disease increases risk because it could prevent a diver from exercising sufficiently to get out of a difficult situation such as being caught in a current. It can be a complex matter to recognize the relevant interactions between diving and medical conditions and to determine their impact on suitability for diving. There may follow an equally complex discussion about whether such interactions impart a disqualifying risk, and this may be influenced by the individual candidate's level of risk acceptance and the extent to which others involved (such as dive partners) might be affected. Guidelines are occasionally published on assessment of diving candidates with risk factors for important comorbidities like cardiovascular disease or who have suffered topical problems such as COVID-19 infection (see "Further Reading" list). Physicians interested in regularly conducting such evaluations should obtain relevant training. Short courses providing relevant training are offered by specialist groups in most countries.

BAROTRAUMA

Barotrauma is essentially tissue injury arising as a result of ambient pressure changes. Middle-ear barotrauma (MEBT) in diving is similar to the problem that may occur during descent from altitude in an airplane, but difficulties with equalizing pressure in the middle ear are exaggerated underwater by both the rapidity and magnitude of pressure change as a diver descends or ascends. Failure to periodically insufflate the middle-ear spaces via the eustachian tubes during descent results in increasing pain. As the P_{amb} increases, the tympanic membrane (TM) may be bruised or even ruptured as it is pushed inward. Negative pressure in the middle ear results in engorgement of blood vessels in the surrounding mucous membranes and leads to effusion or bleeding, which can be associated with a *conductive* hearing loss. MEBT is much less common during ascent because expanding gas in the middle-ear space tends to open the eustachian tube automatically. Barotrauma may also affect the respiratory sinuses, although the sinus ostia are usually widely patent and allow automatic pressure equalization without the need for specific maneuvers. If equalization fails, pain usually results in termination of the dive. Difficulty with equalizing ears or sinuses may respond to oral or nasal decongestants.

Much less commonly, divers may suffer inner ear barotrauma (IEBT). Several explanations have been proposed, of which the most favored holds that forceful attempts to insufflate the middle-ear space by Valsalva maneuvers during descent result in transmission of pressure to the perilymph via the cochlear aqueduct and outward rupture of the round window, which is already under tension because of negative middle-ear pressure. The clinician should be alerted to possible IEBT after diving by a *sensorineural* hearing loss or true vertigo (which is often accompanied by nausea, vomiting, nystagmus, and ataxia). These manifestations can also occur in vestibulocochlear DCS (see below) but should never be attributed to MEBT. Immediate review by an expert diving physician is recommended, and urgent referral to an otologist will often follow.

The lungs are also vulnerable to barotrauma but are at most risk during ascent. If expanding gas becomes trapped in the lungs as P_{amb} falls, this may rupture alveoli and associated vascular tissue. Gas trapping may occur if divers intentionally or involuntarily hold their breath during ascent or if there are bullae. The extent to which asthma predisposes to pulmonary barotrauma is debated, but the presence of active bronchoconstriction must increase risk. For this reason, asthmatics who regularly require bronchodilator medications or whose airways are sensitive to exercise or cold air are usually discouraged from diving. While possible consequences of pulmonary barotrauma include pneumothorax and mediastinal emphysema, the most feared is the introduction of gas into the pulmonary veins leading to cerebral arterial gas embolism (CAGE). Manifestations of CAGE include loss of consciousness, confusion, hemiplegia, visual disturbances, and speech difficulties appearing immediately or within minutes after surfacing. The management is the same as for DCS described below. The natural history of CAGE often includes substantial or complete resolution of symptoms early after the event. This is probably the clinical correlate of bubble involution and redistribution with consequent restoration of flow. Patients exhibiting such remissions should still be reviewed at specialist diving medical centers because secondary deterioration or re-embolization can occur. Unsurprisingly, these events can be misdiagnosed as typical strokes or transient ischemic attacks (TIAs) **(Chap. 427)** when patients are seen by clinicians unfamiliar with diving medicine. *All patients presenting with neurologic symptoms after diving should have their symptoms discussed with a specialist in diving medicine and be considered for recompression therapy.*

DECOMPRESSION SICKNESS

DCS is caused by the formation of bubbles from dissolved inert gas (usually nitrogen) during or after ascent (decompression) from a compressed gas dive. Bubble formation is also possible following decompression for extravehicular activity during space flight and with ascent to altitude in unpressurized aircraft. DCS in the latter scenarios is probably rare in comparison with diving, where the incidence is ~1:10,000 recreational dives.

Breathing at elevated P_{amb} results in increased uptake of inert gas into blood and then into tissues. The rate at which tissue inert gas equilibrates with the inspired inert gas pressure is proportional to tissue blood flow and the blood-tissue partition coefficient for the gas. Similar factors dictate the kinetics of inert gas washout during ascent. If the rate of gas washout from tissues does not match the rate of decline in P_{amb}, then the sum of dissolved gas pressures in the tissue will exceed P_{amb}, a condition referred to as "supersaturation." This is the prerequisite for bubbles to form during decompression, although other less well-understood factors are also involved. Deeper and longer dives result in greater inert gas absorption and greater likelihood of tissue supersaturation during ascent. Divers control their ascent for a given depth and time exposure using algorithms that often include periods where ascent is halted for a prescribed period at different depths to allow time for gas washout ("decompression stops"). Although a breach of these protocols increases the risk of DCS, adherence does not guarantee that it will be prevented. DCS should be considered in any diver manifesting postdive symptoms not readily explained by an alternative mechanism.

Bubbles may form within tissues themselves, where they cause symptoms by mechanical distraction of pain-sensitive or functionally important structures. They also appear in the venous circulation, almost certainly forming in capillary beds as blood passes through supersaturated tissues. Some venous bubbles are tolerated without symptoms and are filtered from the circulation in the pulmonary capillaries. However, in sufficiently large numbers, these bubbles are capable of inciting inflammatory and coagulation cascades, damaging endothelium, activating formed elements of blood such as platelets, and causing symptomatic pulmonary vascular obstruction. Moreover, if there is a right-to-left shunt through a patent foramen ovale (PFO) or an intrapulmonary shunt, then venous bubbles may enter the arterial circulation (25% of adults have a probe-patent PFO). The risk of cerebral, spinal cord, inner ear, and skin manifestations appears higher in the presence of significant shunts, suggesting that these "arterialized" venous bubbles can cause harm, perhaps by disrupting flow in the microcirculation of target organs. Circulating microparticles, which are elevated in number and size after diving, are currently under investigation as indicators of decompression stress and as injurious agents in their own right. How they arise and their exact role in DCS remain unclear.

Table 463-3 lists manifestations of DCS grouped according to organ system. The majority of cases present with mild symptoms, including musculoskeletal pain, fatigue, and minor neurologic manifestations such as patchy paresthesias. Serious presentations are much less common. Pulmonary and cardiovascular manifestations can be life-threatening, and spinal cord involvement frequently results in permanent disability. Latency is variable. Serious DCS usually manifests within minutes of surfacing, but mild symptoms may not appear for several hours. Symptoms arising >24 h after diving are very unlikely to be DCS. The presentation may be confusing and nonspecific, and there are no useful diagnostic investigations. Diagnosis is based on integration of findings from examination of the dive profile, the nature and

TABLE 463-3 Manifestations of Decompression Sickness

ORGAN SYSTEM	MANIFESTATIONS
Musculoskeletal	Limb pain
Neurologic	
Cerebral	Confusion
	Visual disturbances
	Speech disturbances
Spinal	Muscular weakness
	Paralysis
	Upper motor neuron signs
	Bladder and sphincter dysfunction
	Dermatomal sensory disturbances
	Abdominal pain
	Girdle pain
Vestibulocochlear	Hearing loss
	Vertigo and ataxia
	Nausea and vomiting
Peripheral	Patchy nondermatomal sensory disturbance
Pulmonary	Cough
	Dyspnea
Cardiovascular	Hemoconcentration
	Coagulopathy
	Hypotension
Cutaneous	Rash, itch
Lymphatic	Soft tissue edema, often relatively localized
Constitutional	Fatigue and malaise

temporal relationship of symptoms, and the clinical examination. Some DCS presentations may be difficult to separate from CAGE following pulmonary barotrauma, but from a clinical perspective, the distinction is unimportant because the first aid and definitive management of both conditions are the same.

TREATMENT

Diving Medicine

First aid for either DCS or CAGE includes horizontal positioning (especially if there are cerebral manifestations), intravenous fluids if available, and sustained 100% oxygen administration. The latter accelerates inert gas washout from tissues and promotes resolution of bubbles. Definitive treatment of DCS or CAGE with recompression and hyperbaric oxygen is justified in most instances, although some mild or marginal DCS cases may be managed with first aid measures alone—an option that may be invoked by experienced diving physicians under various circumstances, but especially if evacuation for recompression is hazardous or extremely difficult. Long-distance evacuations are usually undertaken using a helicopter flying at low altitude or a fixed-wing air ambulance pressurized to 1 ATA.

Recompression reduces bubble volume in accordance with Boyle's law and increases the inert gas partial pressure difference between a bubble and surrounding tissue. At the same time, oxygen administration markedly increases the inert gas partial pressure difference between alveoli and tissue. The net effect is to significantly increase the rate of inert gas diffusion from bubble to tissue and tissue to blood, thus accelerating bubble resolution. Hyperbaric oxygen also helps oxygenate compromised tissues and may ameliorate some of the proinflammatory effects of bubbles. Various recompression protocols have been advocated, but there are no data that define the optimum approach. Recompression typically begins with oxygen administered at 2.8 ATA, the maximum pressure at which the risk of oxygen toxicity remains acceptable in a hyperbaric chamber. There follows a stepwise decompression over variable periods adjusted to symptom response. The most widely used algorithm is the U.S. Navy Table 6, whose shortest format lasts 4 h and 45 min. Typically, shorter "follow-up" recompressions are repeated daily while symptoms persist and appear responsive to treatment. Adjuncts to recompression include intravenous fluids and other supportive care as necessary. Occasionally, very sick divers require intubation, ventilation, and high-level intensive care.

The presentation of sick divers to physicians or hospitals without diving medicine expertise creates a risk of misinterpretation of nonspecific manifestations and of consequent mistakes in diagnosis and management. Physicians finding themselves in this situation are strongly advised to expeditiously contact the 24-h diving emergency advisory service provided by the Divers Alert Network (DAN). This can be accessed at +1-919-684-9111, and there are subsidiary or related services in virtually all jurisdictions globally.

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464 Hypothermia and Peripheral Cold Injuries

Daniel F. Danzl

HYPOTHERMIA

Accidental hypothermia occurs when there is an unintentional drop in the body's core temperature below 35°C (95°F). At this temperature, many of the compensatory physiologic mechanisms that conserve heat begin to fail. *Primary accidental hypothermia* is a result of the direct exposure of a previously healthy individual to the cold. The mortality rate is much higher for patients who develop *secondary hypothermia* as a complication of a serious systemic disorder or injury.

TABLE 464-1 Risk Factors for Hypothermia

Age extremes	Endocrine-related
Elderly	Diabetes mellitus
Neonates	Hypoglycemia
Environmental exposure	Hypothyroidism
Occupational	Adrenal insufficiency
Sports-related	Hypopituitarism
Inadequate clothing	Neurologic
Immersion	Cerebrovascular accident
Toxicologic and pharmacologic	Hypothalamic disorders
Ethanol	Parkinson's disease
Anesthetics	Spinal cord injury
Antipsychotics	Multisystemic
Antidepressants	Trauma
Anxiolytics	Sepsis
Benzodiazepines	Shock
Neuromuscular blockers	Hepatic or renal failure
Insufficient fuel	Carcinomatosis
Malnutrition	Burns and exfoliative dermatologic disorders
Marasmus	Immobility or debilitation
Kwashiorkor	

CAUSES

Primary accidental hypothermia is geographically and seasonally pervasive. Although most cases occur in the winter months and in colder climates, this condition is surprisingly common in warmer regions as well. Multiple variables render individuals at the extremes of age—both the elderly and neonates—particularly vulnerable to hypothermia (Table 464-1). The elderly have diminished thermal perception and are more susceptible to immobility, malnutrition, and systemic illnesses that interfere with heat generation or conservation. Dementia, psychiatric illness, and socioeconomic factors often compound these problems. Neonates have high rates of heat loss because of their increased surface-to-mass ratio and their lack of effective shivering and adaptive behavioral responses. At all ages, malnutrition can contribute to heat loss because of diminished subcutaneous fat and as a result of depleted energy stores used for thermogenesis.

Individuals whose occupations or hobbies entail extensive exposure to cold weather are at increased risk for hypothermia. Military history is replete with hypothermic tragedies. Hunters, sailors, skiers, and climbers also are at great risk of exposure, whether it involves injury, changes in weather, or lack of preparedness.

Ethanol causes vasodilation (which increases heat loss), reduces thermogenesis and gluconeogenesis, and may impair judgment or lead to obtundation. Some antipsychotics, antidepressants, anxiolytics, benzodiazepines, and other medications reduce centrally mediated vasoconstriction. Many hypothermic patients are admitted to intensive care because of drug overdose. Anesthetics can block shivering responses; these effects are compounded when patients are not insulated adequately in the operating or recovery units.

Several types of endocrine dysfunction cause hypothermia. Hypothyroidism—particularly when extreme, as in myxedema coma—reduces the metabolic rate and impairs thermogenesis and behavioral responses. Adrenal insufficiency and hypopituitarism also increase susceptibility to hypothermia. Hypoglycemia, most commonly caused by insulin or oral hypoglycemic agents, is associated with hypothermia, in part because of neuroglycopenic effects on hypothalamic function. Increased osmolality and metabolic derangements associated with uremia, diabetic ketoacidosis, and lactic acidosis can lead to altered hypothalamic thermoregulation.

Neurologic injury from trauma, cerebrovascular accident, subarachnoid hemorrhage, and a hypothalamic lesion increases susceptibility to hypothermia. Agenesis of the corpus callosum (*Shapiro's syndrome*) is one cause of episodic hypothermia. In this syndrome, profuse perspiration is followed by a rapid fall in temperature. Acute spinal cord injury disrupts the autonomic pathways that lead to shivering and will prevent cold-induced reflex vasoconstrictive responses.

Hypothermia associated with sepsis is a poor prognostic sign. Hepatic failure causes decreased glycogen storage and gluconeogenesis as well as a diminished shivering response. In acute myocardial infarction associated with low cardiac output, hypothermia may be reversed after adequate resuscitation. With extensive burns, psoriasis, erythrodermas, and other skin diseases, increased peripheral-blood flow leads to excessive heat loss.

THERMOREGULATION

Heat loss occurs through five mechanisms: radiation (55–65% of heat loss), conduction (10–15% of heat loss, increased in cold water), convection (increased in the wind), respiration, and evaporation; both of the latter two mechanisms are affected by the ambient temperature and the relative humidity.

The preoptic anterior hypothalamus normally orchestrates thermoregulation (Chap. 18). The immediate defense of thermoneutrality is via the autonomic nervous system, whereas delayed control is mediated by the endocrine system. Autonomic nervous system responses include the release of norepinephrine, increased muscle tone, and shivering, leading to thermogenesis and an increase in the basal metabolic rate. Cutaneous cold thermoreception causes direct reflex vasoconstriction to conserve heat. Prolonged exposure to cold also stimulates the thyroid axis, leading to an increased metabolic rate.

CLINICAL PRESENTATION

In most cases of hypothermia, the history of exposure to environmental factors (e.g., prolonged exposure to the outdoors without adequate clothing) makes the diagnosis straightforward. In urban settings, however, the presentation is often more subtle, and other disease processes, toxin exposures, or psychiatric diagnoses should be considered. Predicting the core temperature based on the clinical presentation is very difficult.

After initial stimulation by hypothermia, there is progressive depression of all organ systems. The timing of the appearance of these clinical manifestations varies widely (Table 464-2). Without knowing the core temperature, it can be difficult to interpret other vital signs. For example, tachycardia disproportionate to the core temperature suggests secondary hypothermia resulting from hypoglycemia, hypovolemia, or a toxin overdose. Because carbon dioxide production declines progressively, the respiratory rate should be low; persistent hyperventilation suggests a central nervous system (CNS) lesion or an organic acidosis. A markedly depressed level of consciousness in a patient with mild hypothermia suggests an overdose or CNS dysfunction due to infection or trauma.

Physical examination findings will also be altered by hypothermia. For instance, the assumption that areflexia is solely attributable to hypothermia can obscure the diagnosis of a spinal cord lesion. Patients with hypothermia may be confused or combative; these symptoms abate more rapidly with rewarming than with chemical or physical restraint. A classic example of maladaptive behavior in patients with hypothermia is paradoxical undressing, which involves the inappropriate removal of clothing in response to a cold stress. The cold-induced ileus and abdominal rectus spasm can mimic or mask the presentation of an acute abdomen (Chap. 15).

When a patient in hypothermic cardiac arrest is first discovered, cardiopulmonary resuscitation (CPR) is indicated unless (1) a do-not-resuscitate status is verified, (2) obviously lethal injuries are identified, or (3) the depression of a frozen chest wall is not possible. Continuous CPR is normally recommended, and interruptions should be avoided if possible. In the field, when the core temperature is <28°C, intermittent CPR may also be effective.

As the resuscitation proceeds, the prognosis is grave if there is evidence of widespread cell lysis, as reflected by potassium levels >10–12 mmol/L (10–12 meq/L). Other findings that may preclude continuing resuscitation include a core temperature <10–12°C (<50–54°F), a pH <6.5, and evidence of intravascular thrombosis with a fibrinogen value <0.5 g/L (<50 mg/dL). The decision to terminate resuscitation

TABLE 464-2 Physiologic Changes Associated with Accidental Hypothermia

SEVERITY	BODY TEMPERATURE	CENTRAL NERVOUS SYSTEM	CARDIOVASCULAR	RESPIRATORY	RENAL AND ENDOCRINE	NEUROMUSCULAR
Mild	35°C (95°F)–32.2°C (90°F)	Linear depression of cerebral metabolism; amnesia; apathy; dysarthria; impaired judgment; maladaptive behavior	Tachycardia, then progressive bradycardia; cardiac cycle prolongation; vasoconstriction; increase in cardiac output and blood pressure	Tachypnea, then progressive decrease in respiratory minute volume; declining oxygen consumption; bronchorrhea; bronchospasm	Diuresis; increase in catecholamines, adrenal steroids, triiodothyronine, and thyroxine; increase in metabolism with shivering	Increased preshivering muscle tone, then fatiguing
Moderate	<32.2°C (90°F)–28°C (82.4°F)	EEG abnormalities; progressive depression of level of consciousness; pupillary dilation; paradoxical undressing; hallucinations	Progressive decrease in pulse and cardiac output; increased atrial and ventricular arrhythmias; suggestive (J-wave) ECG changes	Hypoventilation: 50% decrease in carbon dioxide production per 8°C (17.6°F) drop in temperature; absence of protective airway reflexes	50% increase in renal blood flow; renal autoregulation intact; impaired insulin action	Hyporeflexia; diminishing shivering-induced thermogenesis; rigidity
Severe	<28°C (<82.4°F)	Loss of cerebrovascular autoregulation; decline in cerebral blood flow; coma; loss of ocular reflexes; progressive decrease in EEG abnormalities	Progressive decrease in blood pressure, heart rate, and cardiac output; reentrant dysrhythmias; maximal risk of ventricular fibrillation; asystole	Pulmonic congestion and edema; 75% decrease in oxygen consumption; apnea	Decrease in renal blood flow that parallels decrease in cardiac output; extreme oliguria; poikilothermia; 80% decrease in basal metabolism	No motion; decreased nerve-conduction velocity; peripheral areflexia; no corneal or oculocephalic reflexes

Abbreviations: ECG, electrocardiogram; EEG, electroencephalogram.

Source: From DF Danzl, RS Pozos: Accidental hypothermia. N Engl J Med 331:1756, 1994. Copyright © 1994 Massachusetts Medical Society. Reprinted with permission from Massachusetts Medical Society.

before rewarming the patient past 33°C (91°F) should be predicated on the type and severity of the precipitants of hypothermia. Survival has occurred with a cardiac arrest time over 7 h. There is an ongoing search for validated prognostic indicators for recovery from hypothermia. The Swiss grading system considers core body temperature and the clinical findings. Other scoring systems also consider age, albumin, and lactate levels. A history of asphyxia, as in an avalanche, with secondary cooling is the most important negative predictor of survival.

DIAGNOSIS AND STABILIZATION

Hypothermia is confirmed by measurement of the core temperature, preferably at two sites. Rectal probes should be placed to a depth of 15 cm and not adjacent to cold feces. A simultaneous esophageal probe can be placed 24 cm below the larynx; it may read falsely high during heated inhalation therapy. Relying solely on infrared tympanic thermography is not advisable.

After a diagnosis of hypothermia is established, cardiac monitoring should be instituted, along with attempts to limit further heat loss. If the patient is in ventricular fibrillation, it is unclear at what core temperature ventricular defibrillation (2 J/kg) should first be attempted. One biphasic attempt below 30°C is warranted. Further defibrillation attempts should usually be deferred until some rewarming (1°–2°C) is achieved and ventricular fibrillation is coarser. Although cardiac pacing for hypothermic bradydysrhythmias is rarely indicated, the transthoracic technique is preferable. The J or Osborn wave at the junction of the QRS complex and ST segment suggests the diagnosis. Obvious J waves are routinely misdiagnosed by automated readings as injury current.

Supplemental oxygenation is always warranted, since tissue oxygenation is affected adversely by the leftward shift of the oxyhemoglobin dissociation curve. Pulse oximetry is often unreliable in patients with vasoconstriction. If protective airway reflexes are absent, gentle endotracheal intubation should be performed. Adequate preoxygenation will prevent ventricular arrhythmias.

Insertion of a gastric tube prevents dilation secondary to decreased bowel motility. Indwelling bladder catheters facilitate monitoring of cold-induced diuresis and can provide an ancillary approach for temperature monitoring. Dehydration is encountered commonly with chronic hypothermia, and most patients benefit from an intravenous or intraosseous crystalloid bolus. Normal saline is preferable to lactated Ringer's solution, as the liver in hypothermic patients inefficiently metabolizes lactate. The placement of a pulmonary artery catheter can cause perforation of the less compliant pulmonary artery. Insertion of a central venous catheter deeply into the cold right atrium should be avoided since this procedure, similar to transvenous pacing, can precipitate refractory arrhythmias.

Arterial blood gases should *not* be corrected for temperature **(Chap. 55)**. An uncorrected pH of 7.42 and a P_{CO_2} of 40 mmHg reflect appropriate alveolar ventilation and acid-base balance at any core temperature. Acid-base imbalances should be corrected gradually, since the bicarbonate buffering system is inefficient. A common error is overzealous hyperventilation in the setting of depressed CO_2 production. When the P_{CO_2} decreases by 10 mmHg at 28°C (82°F), it doubles the pH increase of 0.08 that occurs at 37°C (99°F).

The severity of anemia may be underestimated because the hematocrit increases 2% for each 1°C drop in temperature. White blood cell sequestration and bone marrow suppression are common, potentially masking an infection. Although hypokalemia is more common in chronic hypothermia, hyperkalemia also occurs; the expected electrocardiographic changes are often obscured by hypothermia. Patients with renal insufficiency, metabolic acidosis, or rhabdomyolysis are at greatest risk for electrolyte disturbances.

Coagulopathies are common because cold inhibits the enzymatic reactions required for activation of the intrinsic cascade. In addition, thromboxane B_2 production by platelets is temperature dependent, and platelet function is impaired. The administration of platelets and fresh-frozen plasma is therefore not effective. Coagulation studies can be deceptively normal and contrast with the observed in vivo coagulopathy. This contradiction occurs because all coagulation tests are routinely performed at 37°C (99°F), and the enzymes are thus rewarmed.

REWARMING STRATEGIES

The key initial decision is whether to rewarm the patient passively or actively. *Passive external rewarming* simply involves covering and insulating the patient in a warm environment. With the head also covered, the rate of rewarming is usually 0.5°–2°C (1.10°–4.4°F) per hour. This technique is ideal for previously healthy patients who develop acute, mild primary accidental hypothermia. The patient must have sufficient glycogen to support endogenous thermogenesis.

The application of heat directly to the extremities of patients with chronic severe hypothermia should be avoided because it can induce peripheral vasodilation and precipitate core temperature "afterdrop," a response characterized by a continual decline in the core temperature

after removal of the patient from the cold. Truncal heat application reduces the risk of afterdrop.

Active rewarming is necessary under the following circumstances: core temperature <32°C (<90°F) (*poikilothermia*), cardiovascular instability, age extremes, CNS dysfunction, hormone insufficiency, and suspicion of secondary hypothermia. *Active external rewarming* is best accomplished with forced-air heating blankets. Other options include devices that circulate water through external heat exchange pads, radiant heat sources, and hot packs. Monitoring a patient with hypothermia in a heated tub is extremely difficult. Electric blankets should be avoided because vasoconstricted skin is easily burned.

There are numerous widely available options for *active core rewarming*. Airway rewarming with heated humidified oxygen (40°–45°C [104°–113°F]) via mask or endotracheal tube is a convenient option. Although airway rewarming provides less heat than do some other forms of active core rewarming, it eliminates respiratory heat loss and adds 1°–2°C (2.2°–4.4°F) to the overall rewarming rate. Crystalloids should be heated to 40°–42°C (104°–108°F), but the quantity of heat provided is significant only during massive volume resuscitation. The most efficient method for heating and delivering fluid or blood is with a countercurrent in-line heat exchanger. Heated irrigation of the gastrointestinal tract or bladder transfers minimal heat because of the limited available surface area. These methods should be reserved for patients in cardiac arrest and then used in combination with all available active rewarming techniques.

Closed thoracic lavage is far more efficient in severely hypothermic patients with cardiac arrest. The hemithoraxes are irrigated through two inserted large-bore thoracostomy tubes. Thoracostomy tubes should not be placed in the left chest of a spontaneously perfusing patient for purposes of rewarming. Peritoneal lavage with the dialysate at 40°–45°C (104°–113°F) efficiently transfers heat when delivered through two catheters with outflow suction. Like peritoneal dialysis, standard hemodialysis is especially useful for patients with electrolyte abnormalities, rhabdomyolysis, or toxin ingestion. Another option involves the use of endovascular temperature control catheters.

Extracorporeal blood rewarming options **(Table 464-3)** should be considered in severely hypothermic patients, especially those with *primary accidental hypothermia*. Extracorporeal life support, including bypass, should be considered in nonperfusing patients without documented contraindications to resuscitation. Circulatory support may be the only effective option in patients with completely frozen extremities or those with significant tissue destruction coupled with rhabdomyolysis. There is no evidence that extremely rapid rewarming improves survival in perfusing patients.

TABLE 464-3 Options for Extracorporeal Blood Rewarming

EXTRACORPOREAL REWARMING TECHNIQUE	CONSIDERATIONS
Continuous venovenous (CVV) rewarming	Circuit: CV catheter to CV, dual-lumen CV, or peripheral catheter No oxygenator/circulatory support Flow rates 150–400 mL/min ROR 2°–3°C (4.4°–6.6°F)/h
Hemodialysis	Circuit: single- or dual-vessel cannulation Stabilizes electrolyte or toxicologic abnormalities Exchange cycle volumes 200–500 mL/min ROR 2°–3°C (4.4°–6.6°F)/h
Continuous arteriovenous rewarming (CAVR)	Circuit: percutaneous 8.5-Fr femoral catheters Requires systolic blood pressure of 60 mmHg No perfusionist/pump/anticoagulation Flow rates 225–375 mL/min ROR 3°–4°C (6.6°–8.8°F)/h
Cardiopulmonary bypass (CPB)	Circuit: full circulatory support with pump and oxygenator Perfusate-temperature gradient 5°–10°C (11°–22° F) Flow rates 2–7 L/min (average 3–4 L/min) ROR up to 9.5°C (20.9°F)/h
Venoarterial extracorporeal membrane oxygenation (VA-ECMO)	Decreased risk of post-rewarming cardiorespiratory failure Improved neurologic outcome

Abbreviations: CV, central venous; ROR, rate of rewarming.

TREATMENT

Hypothermia

When a patient is hypothermic, target organs and the cardiovascular system respond minimally to most medications. Generally, medications are withheld below 30°C (86°F). In contrast to antiarrhythmics, low-dose vasopressor medications may improve the intra-arrest rates of return of spontaneous circulation. Because of increased binding of drugs to proteins as well as impaired metabolism and excretion, either a lower dose or a longer interval between doses should be used to avoid toxicity. As an example, the administration of repeated doses of digoxin or insulin would be ineffective while the patient is hypothermic, but the residual drugs would be potentially toxic during rewarming.

Achieving a mean arterial pressure of at least 60 mmHg should be an early objective. If the hypotension is disproportionate for temperature and does not respond to crystalloid/colloid infusion and rewarming, low-dose dopamine support (2–5 μg/kg per min) should be considered. Perfusion of the vasoconstricted cardiovascular system also may improve with low-dose IV nitroglycerin.

Atrial arrhythmias should be monitored initially without intervention, as the ventricular response should be slow and, unless preexistent, most will convert spontaneously during rewarming. The role of prophylaxis and treatment of ventricular arrhythmias is complex. Preexisting ventricular ectopy may be suppressed by hypothermia and reappear during rewarming. None of the class I agents is proven to be safe and efficacious.

Initiating empirical therapy for adrenal insufficiency usually is not warranted unless the history suggests steroid dependence or hypoadrenalism or efforts to rewarm with standard therapy fail. The administration of parenteral levothyroxine to euthyroid patients with hypothermia, however, is potentially hazardous. Because laboratory results can be delayed and confounded by the presence of the sick euthyroid syndrome **(Chap. 382)**, historic clues or physical findings suggestive of hypothyroidism should be sought. When myxedema is the cause of hypothermia, the relaxation phase of the Achilles reflex is prolonged more than is the contraction phase.

Hypothermia obscures most of the symptoms and signs of infection, notably fever and leukocytosis. Shaking rigors from infection may be mistaken for shivering. Except in mild cases, extensive cultures and repeated physical examinations are essential. Unless an infectious source is identified, empirical antibiotic prophylaxis is most warranted in the elderly, neonates, and immunocompromised patients.

FROSTBITE

Peripheral cold injuries include both freezing and nonfreezing injuries to tissue. Tissue freezes quickly when in contact with thermal conductors such as metal and volatile solutions. Other predisposing factors include constrictive clothing or boots, immobility, and vasoconstrictive medications. Frostbite occurs when the tissue temperature drops below 0°C (32°F). Ice-crystal formation subsequently distorts and destroys the cellular architecture. Once the vascular endothelium is damaged, stasis progresses rapidly to microvascular thrombosis. After the tissue thaws, there is progressive dermal ischemia. The microvasculature begins to collapse, arteriovenous shunting increases tissue pressures, and edema forms. Finally, thrombosis, ischemia, and superficial necrosis appear. The development of mummification and demarcation may take weeks to months.

CLINICAL PRESENTATION

The initial presentation of frostbite can be deceptively benign. The symptoms always include a sensory deficiency affecting light touch, pain, or temperature perception. The acral areas and distal extremities are the most common insensate areas. Some patients describe a clumsy or "chunk of wood" sensation in the extremity.

Deep frostbitten tissue can appear waxy, mottled, yellow, or violaceous-white. Favorable presenting signs include some warmth or sensation with normal color. The injury is often superficial if the subcutaneous tissue is pliable or if the dermis can be rolled over bony prominences.

Clinically, frostbite is superficial or deep. Superficial frostbite does not entail tissue loss but rather causes only anesthesia and erythema. The appearance of vesiculation surrounded by edema and erythema implies deeper involvement **(Fig. 464-1)**. Hemorrhagic vesicles reflect a serious injury to the microvasculature and indicate severe frostbite. Damages in subcuticular, muscular, or osseous tissues may result in amputation. An alternative classification establishes grades based on the location of presenting cyanosis; that is grade 1, absence of cyanosis; grade 2, cyanosis on the distal phalanx; grade 3, cyanosis up to the metacarpophalangeal (MP) joint; and grade 4 cyanosis proximal to the MP joint.

The two most common nonfreezing peripheral cold injuries are *chilblain* (*pernio*) and *immersion* (*trench*) *foot*. Chilblain results from neuronal and endothelial damage induced by repetitive exposure to damp cold above the freezing point. Young females, particularly those with a history of Raynaud's phenomenon, are at greatest risk. Persistent vasospasticity and vasculitis can cause erythema, mild edema, and pruritus. Eventually plaques, blue nodules, and ulcerations develop. These lesions typically involve the dorsa of the hands and feet. In contrast, immersion foot results from repetitive exposure to wet cold above the freezing point. The feet initially appear cyanotic, cold, and edematous. The subsequent development of bullae is often indistinguishable from frostbite. This vesiculation rapidly progresses to ulceration and liquefaction gangrene. Patients with milder cases report hyperhidrosis, cold sensitivity, and painful ambulation for many years.

FIGURE 464-1 Frostbite with vesiculation, surrounded by edema and erythema.

TREATMENT

Peripheral Cold Injuries

When frostbite accompanies hypothermia, hydration may improve vascular stasis. Frozen tissue should be thawed rapidly and completely by immersion in circulating water at 37°–40°C (99°–104°F) for 30–60 min and not by using hot air. Rapid rewarming often produces an initial hyperemia. The early formation of large clear distal blebs is more favorable than that of smaller proximal dark hemorrhagic blebs. A common error is the premature termination of thawing, since the reestablishment of perfusion is intensely painful. Parenteral narcotics will be necessary with deep frostbite. If cyanosis persists after rewarming, the tissue compartment pressures should be monitored carefully.

Many antithrombotic and vasodilatory treatment regimens have been evaluated. The prostacyclin analogue iloprost given within 48 h after rewarming is an option. There is no conclusive evidence that sympathectomy, steroids, calcium channel blockers, or hyperbaric oxygen salvages tissue.

Patients who have deep frostbite injuries with the potential for significant morbidity should be considered for intravenous or intraarterial thrombolytic therapy. Angiography or pyrophosphate scanning may help evaluate the injury and monitor the progress of tissue plasminogen activator therapy (rt-PA). Heparin is recommended as adjunctive therapy. Intraarterial thrombolysis may reduce the need for digital and more proximal amputations when administered within 24 h of severe injuries. A treatment protocol for frostbite is summarized in **Table 464-4**.

Unless infection develops, any decision regarding debridement or amputation should generally be deferred. Angiography or

TABLE 464-4 Treatment for Frostbite

BEFORE THAWING	DURING THAWING	AFTER THAWING
Remove from environment.	Consider parenteral analgesia and ketorolac.	Gently dry and protect part; elevate; place pledgets between toes, if macerated.
Prevent partial thawing and refreezing.	Administer ibuprofen (400 mg PO).	If clear vesicles are intact, aspirate sterilely; if broken, debride and dress with antibiotic or sterile aloe vera ointment.
Stabilize core temperature and treat hypothermia.	Immerse part in 37°–40°C (99°–104°F) (thermometer-monitored) circulating water containing an antiseptic soap until distal flush (10–45 min).	Leave hemorrhagic vesicles intact to prevent desiccation and infection.
Protect frozen part—no friction or massage.	Encourage patient to gently move part.	Continue ibuprofen (400–600 mg PO [12 mg/kg per day] q8 to 12h).
Address medical or surgical conditions.	If pain is refractory, reduce water temperature to 35°–37°C (95°–99°F) and administer parenteral narcotics.	Consider tetanus and streptococcal prophylaxis; elevate part. Administer hydrotherapy at 37°C (99°F). Consider dextran or phenoxybenzamine or, in severe cases, thrombolysis rt-PA (IV or intraarterial).

Abbreviation: rt-PA, recombinant tissue plasminogen activator.

technetium-99 bone scan may assist in the determination of surgical margins. Magnetic resonance angiography may also demonstrate the line of demarcation earlier than does clinical demarcation.

The most common symptomatic sequelae reflect neuronal injury and persistently abnormal sympathetic tone, including paresthesia, thermal misperception, and hyperhidrosis. Delayed findings include nail deformities, cutaneous carcinomas, and epiphyseal damage in children.

Management of the chilblain syndrome is usually supportive. With refractory perniosis, alternatives include nifedipine, steroids, and limaprost, a prostaglandin E_1 analogue.

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465 Heat-Related Illnesses

Daniel F. Danzl

Heat-related illnesses include a spectrum of disorders ranging from heat syncope, muscle cramps, and heat exhaustion to medical emergencies such as heatstroke. The core body temperature is normally maintained within a very narrow range. Although significant levels of hypothermia are tolerated **(Chap. 464)**, multiorgan dysfunction occurs rapidly at temperatures >41°–43°C. In contrast to heatstroke, the far more common sign of fever reflects intact thermoregulation.

THERMOREGULATION

Humans are capable of significant heat generation. Strenuous exercise can increase heat generation twentyfold. The heat load from metabolic heat production and environmental heat absorption is balanced by a variety of heat dissipation mechanisms. These central integrative dissipation pathways are orchestrated by the central thermostat, which is located in the preoptic nucleus of the anterior hypothalamus. Efferent signals sent via the autonomic nervous system trigger cutaneous vasodilation and diaphoresis to facilitate heat loss.

Normally, the body dissipates heat into the environment via four mechanisms. The *evaporation* of skin moisture is the single most efficient mechanism of heat loss but becomes progressively ineffective as the relative humidity rises to >70%. The *radiation* of infrared electromagnetic energy directly into the surrounding environment occurs continuously. (Conversely, radiation is a major source of heat gain in hot climates.) *Conduction*—the direct transfer of heat to a cooler object—and *convection*—the loss of heat to air currents—become ineffective when the environmental temperature exceeds the skin temperature.

Factors that interfere with the evaporation of diaphoresis significantly increase the risk of heat illness. Examples include dripping of sweat off the skin, constrictive or occlusive clothing, dehydration, and excessive humidity. While air is an effective insulator, the thermal conductivity of water is 25 times greater than that of air at the same temperature. The *wet-bulb globe temperature* is a commonly used index to assess the environmental heat load. This calculation considers the ambient air temperature, the relative humidity, and the degree of radiant heat.

The regulation of this heat load is complex and involves the central nervous system (CNS), thermosensors, and thermoregulatory effectors. The central thermostat activates the effectors that produce peripheral vasodilation and sweating. The skin surface is in effect the radiator and the principal location of heat loss, since skin blood flow can increase 25–30 times over the basal rate. This dramatic increase in skin blood flow, coupled with the maintenance of peripheral vasodilation, efficiently radiates heat. At the same time, there is a compensatory vasoconstriction of the splanchnic and renal beds.

Acclimatization to heat reflects a constellation of physiologic adaptations that permit the body to lose heat more efficiently. This process often requires one to several weeks of exposure and work in a hot environment. During acclimatization, the thermoregulatory set point is altered, and this alteration affects the onset, volume, and content of diaphoresis. The threshold for the initiation of sweating is lowered, and the amount of sweat increases, with a lowered salt concentration. Sweating rates can be 1–2 L/h in acclimated individuals during heat stress. Plasma volume expansion also occurs and improves cutaneous vascular flow. The heart rate lowers, with a higher stroke volume. After the individual leaves the hot environment, improved tolerance to heat stress dissipates rapidly, the plasma volume decreases, and deacclimatization occurs within weeks.

PREDISPOSING FACTORS AND DIFFERENTIAL DIAGNOSIS

When there is an excessive heat load, unacclimated individuals can develop a variety of heat-related illnesses. Heat waves exacerbate the mortality rate, particularly among the elderly and among persons lacking adequate nutrition and access to air-conditioned environments. Secondary vascular events, including cerebrovascular accidents and myocardial infarctions, occur at least 10 times more often in conditions of extreme heat.

Exertional heat illness continues to occur when laborers, military personnel, or athletes exercise strenuously in the heat. In addition to the very young and very old, preadolescents and teenagers are at risk since they may use poor judgment when vigorously exercising in high humidity and heat. Other risk factors include obesity, poor conditioning with lack of acclimatization, and mild dehydration.

Cardiovascular inefficiency is a common feature of heat illness. Any physiologic or pharmacologic impediment to cutaneous perfusion impairs heat loss. Many patients are unaware of the heat risk associated with their medications. Anticholinergic agents impair sweating and blunt the normal cardiovascular response to heat. Phenothiazines and heterocyclic antidepressants also have anticholinergic properties that interfere with the function of the preoptic nucleus of the anterior hypothalamus due to central depletion of dopamine.

Calcium channel blockers, beta blockers, and various stimulants also inhibit sweating by reducing peripheral blood flow. To maintain the mean arterial blood pressure, increased cardiac output must be capable of compensating for progressive dehydration. A variety of stimulants and substances of abuse also increase muscle activity and heat production.

Careful consideration of the differential diagnosis is important in the evaluation of a patient for a potential heat-related illness. The clinical setting may suggest other etiologies, such as malignant hyperthermia after general anesthesia. Neuroleptic malignant syndrome can be triggered by certain antipsychotic medications, including selective serotonin reuptake inhibitors. A variety of infectious and endocrine disorders as well as toxicologic or CNS etiologies may mimic heatstroke **(Table 465-1)**.

MINOR HEAT-EMERGENCY SYNDROMES

Heat edema is characterized by mild swelling of the hands, feet, and ankles during the first few days of significant heat exposure. The principal mechanism involves cutaneous vasodilation and pooling of interstitial fluid in response to heat stress. Heat also increases the secretion

TABLE 465-1 Heat-Related Illness: Predisposing Factors and Differential Diagnosis

ILLNESS	PREDISPOSING FACTORS
Cardiovascular inefficiency	Age extremes Beta/calcium channel blockade Congestive heart failure Dehydration Diuresis Obesity Poor physical fitness
Central nervous system illness	Cerebellar injury Cerebral hemorrhage Hypothalamic cerebrovascular accident Psychiatric disorders Status epilepticus
Impaired heat loss	Antihistamines Heterocyclic antidepressants Occlusive clothing Skin abnormalities
Endocrine and immune-related illness	Diabetic ketoacidosis Multiple-organ dysfunction syndrome Pheochromocytoma Systemic inflammatory response syndrome Thyroid storm
Excessive heat load	Environmental conditions Exertion Fever Hypermetabolic state Lack of acclimatization
Infectious illness	Cerebral abscess Encephalitis Malaria Meningitis Sepsis syndrome Tetanus Typhoid
Toxicologic illness	Amphetamines Anticholinergic toxidrome Cocaine Dietary supplements Hallucinogens Malignant hyperthermia Neuroleptic malignant syndrome Salicylates Serotonin syndrome Strychnine Sympathomimetics Withdrawal syndromes (ethanol, hypnotics)

of antidiuretic hormone and aldosterone. Systemic causes of edema, including cirrhosis, nephrotic syndrome, and congestive heart failure, can usually be excluded by the history and physical examination. Heat edema generally resolves without treatment in several days. Simple leg elevation or compression stockings will usually suffice. Diuretics are *not* effective and, in fact, predispose to volume depletion and the development of more serious heat-related illnesses.

Prickly heat (*miliaria rubra*, *lichen tropicus*) is a maculopapular, pruritic, erythematous rash that commonly occurs in clothed areas. Blockage of the sweat pores by debris from macerated stratum corneum causes inflammation in the sweat ducts. As the ducts dilate, they rupture and produce superficial vesicles. The predominant symptom is pruritus. In addition to antihistamines, chlorhexidine in a light cream or lotion provides some relief. In adults, localized areas may benefit from 1% salicylic acid TID, with caution taken to avoid salicylate intoxication. Clothing with breathable fabric should be clean and loose fitting, and activities or environments that induce diaphoresis should be avoided.

Heat syncope (exercise-associated collapse) can follow endurance exercise or occur in the elderly. Other common clinical scenarios include prolonged standing while stationary in the heat and sudden standing after prolonged exposure to heat. Heat stress routinely causes relative volume depletion, decreased vasomotor tone, and peripheral vasodilation. The cumulative effect of this decrease in venous return is postural hypotension, especially in nonacclimated elderly individuals. Many of those affected also have comorbidities. Therefore, other cardiovascular, neurologic, and metabolic causes of syncope should be considered. After removal from the heat source, most patients will recover promptly with cooling and rehydration.

Hyperventilation tetany occurs in some individuals when exposure to heat stimulates hyperventilation, producing respiratory alkalosis, paresthesia, and carpopedal spasm. Unlike heat cramps, heat tetany causes very little muscle-compartment pain. Treatment includes providing reassurance, moving the patient out of the heat, and addressing the hyperventilation.

HEAT CRAMPS

Heat cramps (exercise-associated muscle cramps) are intermittent, painful, and involuntary spasmodic contractions of skeletal muscles. They typically occur in an unacclimated individual who is at rest after vigorous exertion in a humid, hot environment. In contrast, cramps that occur in athletes during exercise last longer, are relieved by stretching and massage, and resolve spontaneously.

Of note, not all muscle cramps are related to exercise, and the differential diagnosis includes many other disorders. A variety of medications, myopathies, endocrine disorders, and sickle cell trait are other possible causes.

The typical patient with heat cramps is usually profusely diaphoretic and has been replacing fluid losses with copious water or other hypotonic fluids. Roofers, firefighters, military personnel, athletes, steel workers, and field workers are commonly affected. Other predisposing factors include insufficient sodium intake before intense activity in the heat and lack of heat acclimatization, resulting in sweat with a high salt concentration.

The precise pathogenesis of heat cramps appears to involve a relative deficiency of sodium, potassium, and fluid at the intracellular level. Coupled with copious hypotonic fluid ingestion, large amounts of sodium in the diaphoresis cause hyponatremia and hypochloremia, resulting in muscle cramps due to calcium-dependent muscle relaxation. Total-body depletion of potassium may be observed during the period of heat acclimatization. Rhabdomyolysis is very rare with routine exercise-associated muscle cramps.

Heat cramps that are not accompanied by significant dehydration can be treated with commercially available electrolyte solutions. Although the flavored electrolyte solutions are far more palatable, two 650-mg salt tablets dissolved in 1 quart of water produce a 0.1% saline solution. Individuals should avoid the ingestion of undissolved salt tablets, which are a gastric irritant and may induce vomiting.

HEAT EXHAUSTION

The physiologic hallmarks of heat exhaustion—in contrast to heatstroke—are the maintenance of thermoregulatory control and CNS function. The core temperature is usually elevated but is generally <40.5°C (<105°F). The two physiologic precipitants are water depletion and sodium depletion, which often occur in combination. Laborers, athletes, and elderly individuals exerting themselves in hot environments, without adequate fluid intake, tend to develop *water-depletion heat exhaustion*. Persons working in the heat frequently consume only two-thirds of their net water loss and are voluntarily dehydrated. In contrast, *salt-depletion heat exhaustion* occurs more slowly in unacclimated persons who have been consuming large quantities of hypotonic solutions.

Heat exhaustion is usually a diagnosis of exclusion because of the multitude of nonspecific symptoms. If any signs of heatstroke are present, rapid cooling and crystalloid resuscitation should be initiated immediately during stabilization and evaluation. Mild neurologic and gastrointestinal influenza-like symptoms are common. These symptoms may include headache, vertigo, ataxia, impaired judgment, malaise, dizziness, nausea, and muscle cramps. Orthostatic hypotension and sinus tachycardia develop frequently. More significant CNS impairment suggests heatstroke or other infectious, neurologic, or toxicologic diagnoses.

Hemoconcentration does not always develop, and rapid infusion of isotonic IV fluids should be guided by frequent electrolyte determinations and perfusion requirements. Most cases of heat exhaustion reflect mixed sodium and water depletion. Sodium-depletion heat exhaustion is characterized by hyponatremia and hypochloremia. Hepatic aminotransferases are mildly elevated in both types of heat exhaustion. Urinary sodium and chloride concentrations are usually low.

Some patients with heat exhaustion develop heatstroke after removal from the heat-stress environment. Aggressive cooling of nonresponders is indicated until their core temperature is 39°C (102.2°F). Except in mild cases, free water deficits should be replaced slowly over 24–48 h to avoid a decrease of serum osmolality by >2 mOsm/h.

The disposition of younger, previously healthy heat-exhaustion patients who have no major laboratory abnormalities may include hospital observation and discharge after IV rehydration. Older patients with comorbidities (including cardiovascular disease) or predisposing factors often require inpatient fluid and electrolyte replacement, monitoring, and reassessment.

HEATSTROKE

The clinical manifestations of heatstroke reflect a total loss of thermoregulatory function. Typical vital-sign abnormalities include tachypnea, various tachycardias, hypotension, and a widened pulse pressure. Although there is no single specific diagnostic test, the historical and physical triad of exposure to a heat stress, CNS dysfunction, and a core temperature >40.5°C helps establish the preliminary diagnosis. Some patients with impending heatstroke will initially appear lucid. The definitive diagnosis should be reserved until the other potential causes of hyperthermia are excluded. Many of the usual laboratory abnormalities seen with heatstroke overlap with other conditions. If the patient's mental status does not improve with cooling, toxicologic screening may be indicated, and cranial CT and spinal fluid analysis can be considered.

The premonitory clinical characteristics may be nonspecific and include weakness, dizziness, disorientation, ataxia, and gastrointestinal or psychiatric symptoms. These prodromal symptoms often resemble heat exhaustion. The sudden onset of heatstroke occurs when the maintenance of adequate perfusion requires peripheral vasoconstriction to stabilize the mean arterial blood pressure. As a result, the cutaneous radiation of heat ceases. At this juncture, the core temperature rises dramatically. Since many patients with heatstroke also meet the criteria for systemic inflammatory response syndrome (SIRS) and have a broad differential diagnosis, rapid cooling is essential during the extensive diagnostic evaluation. Heat-induced SIRS reflects the responses of both the innate and the adaptive immune systems (Table 465-1).

There are two forms of heatstroke with significantly different manifestations **(Table 465-2)**. Classic (epidemic) heatstroke (CHS) usually occurs during long periods of high ambient temperature and humidity, as during summer heat waves. Patients with CHS commonly have chronic diseases that predispose to heat-related illness, and they may have limited access to oral fluids. Heat dissipation mechanisms are overwhelmed by both endogenous heat production and exogenous heat stress. Patients with CHS are often compliant with prescribed medications that can impair tolerance to a heat stress. In many of these dehydrated CHS patients, sweating has ceased and the skin is hot and dry.

If cooling is delayed, severe hepatic dysfunction, renal failure, disseminated intravascular coagulation, and fulminant multisystem organ failure may occur. Hepatocytes are very heat sensitive. On presentation, the serum level of aspartate aminotransferase (AST) is routinely elevated. Eventually, levels of both AST and alanine aminotransferase (ALT) often increase to >100 times the normal values. Coagulation studies commonly demonstrate decreased platelets, fibrinogen, and prothrombin. Most patients with CHS require cautious crystalloid resuscitation, electrolyte monitoring, and—in certain refractory cases—consideration of central venous pressure (CVP) measurements. Hypernatremia is secondary to dehydration in CHS. Many patients exhibit significant stress leukocytosis, even in the absence of infection.

TABLE 465-2 Typical Manifestations of Heatstroke

CLASSIC	EXERTIONAL
Older patient	Younger patient
Predisposing health factors/ medications	Healthy condition
Epidemiology (heat waves)	Sporadic cases
Sedentary	Exercising
Anhidrosis (possible)	Diaphoresis (common)
Central nervous system dysfunction	Myocardial/hepatic injury
Oliguria	Acute renal failure
Coagulopathy (mild)	Disseminated intravascular coagulation
Mild lactic acidosis	Marked lactic acidosis
Mild creatine kinase elevation	Rhabdomyolysis
Normoglycemia/calcemia	Hypoglycemia/calcemia
Normokalemia	Hyperkalemia
Normonatremia	Hyponatremia

Patients with exertional heatstroke (EHS), in contrast to those with CHS, are often young and previously healthy, and their diagnosis is usually more obvious from the history. Athletes, laborers, and military recruits are common victims. Unlike those with CHS, many EHS patients present profusely diaphoretic despite significant dehydration. As a result of muscular exertion, rhabdomyolysis and acute renal failure are more common in EHS. Studies to detect rhabdomyolysis and its complications, including hypocalcemia and hyperphosphatemia, should be considered. Hyponatremia, hypoglycemia, and coagulopathies are frequent findings. Elevated creatine kinase and lactate dehydrogenase levels also suggest EHS. Oliguria is a common finding. Renal failure can result from direct thermal injury, untreated rhabdomyolysis, or volume depletion. Common urinalysis findings include microscopic hematuria, myoglobinuria, and granular or red cell casts.

With both CHS and EHS, heat-related increases in cardiac biomarker levels may be present and reversible. Heatstroke often causes thermal cardiomyopathy. As a result, the CVP may be elevated despite significant dehydration. In addition, the patient often presents with potentially deceptive noncardiogenic pulmonary edema and basilar rales despite being significantly hypovolemic. The electrocardiogram commonly displays a variety of tachyarrhythmias, nonspecific ST-T wave changes, and heat-related ischemia or infarction. Rapid cooling—not the *initial* administration of antiarrhythmic medications—is essential.

Above 42°C (107.6°F), heat can rapidly produce direct cellular injury. Thermosensitive enzymes become nonfunctional, and eventually, there is irreversible uncoupling of oxidative phosphorylation. The production of heat-shock proteins increases, and cytokines mediate a systemic inflammatory response. The vascular endothelium is also damaged, and this injury activates the coagulation cascade. Significant shunting away from the splanchnic circulation produces gastrointestinal ischemia. Endotoxins further impair normal thermoregulation. As a result, if cooling is delayed, severe hepatic dysfunction, permanent renal failure, disseminated intravascular coagulation, and fulminant multisystem organ failure may occur.

COOLING STRATEGIES

Before cooling is initiated, endotracheal intubation and continuous core-temperature monitoring should be considered. Peripheral methods to measure temperature are *not* reliable. Hypoglycemia is

a frequent finding and can be addressed by glucose infusion. Since peripheral vasoconstriction delays heat dissipation, repeated administration of discrete boluses of isotonic crystalloid for hypotension is preferable to the administration of α-adrenergic agonists.

Evaporative cooling is frequently the most practical and effective technique. Rapid cooling is essential in both CHS and EHS, and an immediate improvement in vital signs and mental status may prove valuable for diagnostic purposes. Cool water (15°C [60°F]) is sprayed on the exposed skin while fans direct continuous airflow over the moistened skin. Cold packs applied to the neck, axillae, and groin are useful cooling adjuncts. If cardiac electrodes will not adhere, they can be applied to the patient's back.

Immersion cooling in ice-cold water is an alternative option in EHS but can induce peripheral vasoconstriction and shivering. The initial increase in temperature from peripheral vasoconstriction will rapidly be overcome by the large conductive thermal transfer into cold water. This technique presents significant monitoring and resuscitation challenges in many clinical settings. The safety of immersion cooling is best established for young, previously healthy patients with EHS (but not for those with CHS). To avoid hypothermic afterdrop (continued cooling after immersion), active cooling should be terminated at ~38°–39°C (100.4°F–102.2°F).

Cooling with commercially available cooling blankets should not be the sole technique used, since the rate of cooling is far too slow. Other methods are less efficacious and rarely indicated, such as IV infusion of cold fluids and cold irrigation of the bladder or gastrointestinal tract. Cold thoracic and peritoneal lavage are efficient maneuvers but are invasive and rarely necessary. Endovascular cooling also provides effective cooling.

RESUSCITATION

Aspiration commonly occurs in heatstroke, and endotracheal intubation is usually necessary. Depolarizing agents should be avoided. The metabolic demands are high, and supplemental oxygenation is essential due to hypoxemia induced by thermal stress and pulmonary dysfunction. The oxyhemoglobin dissociation curve is shifted to the right. Pneumonitis, pulmonary infarction, hemorrhage, edema, and acute respiratory distress syndrome occur frequently in heatstroke patients. Seizures are common and can occur during therapeutic cooling. Cold induced tonic-clonic muscular rigidity mimics seizure activity.

The circulatory fluid requirements, particularly in CHS, may be deceptively modest. Aggressive cooling and modest volume repletion usually elevate the CVP to 12–14 mmHg. The reading, however, may be deceptive. Many patients present with a thermally induced hyperdynamic circulation accompanied by a high cardiac index, low peripheral vascular resistance, and an elevated CVP caused by right-sided heart failure. In contrast, most patients with EHS require far more zealous isotonic crystalloid resuscitation.

The hypotension that is initially common among patients with heatstroke results from both dehydration and high-output cardiac failure caused by peripheral vasodilation. Inotropes causing α-adrenergic stimulation (e.g., norepinephrine) can impede cooling by causing significant vasoconstriction. Vasoactive catecholamines such as dopamine or dobutamine may be necessary if the cardiac output remains depressed despite an elevated CVP, particularly in patients with a hyperdynamic circulation.

A wide variety of tachyarrhythmias are routinely observed on presentation and usually resolve spontaneously during cooling. The administration of atrial or ventricular antiarrhythmic medications is rarely indicated during cooling. Anticholinergic medications (including atropine) inhibit sweating and should be avoided. With a cardiac rhythm that sustains perfusion, electrical cardioversion of the hyperthermic myocardium should be deferred until the myocardium is cooled. Significant shivering, discomfort, or extreme agitation is preferably mitigated with short-acting benzodiazepines, which are ideal due to their renal clearance. On the other hand, chlorpromazine may lower the seizure threshold, has anticholinergic properties, and can exacerbate the hypotension or cause neuroleptic malignant syndrome. With hepatic dysfunction, barbiturates should be avoided and seizures treated with benzodiazepines.

Coagulopathies more commonly occur after the first day of illness. After cooling, the patient should be monitored for disseminated intravascular coagulation, and replacement therapy with fresh-frozen plasma and platelets should be considered.

There is no therapeutic role for antipyretics in the control of environmentally induced hyperthermia; these drugs block the actions of pyrogens at hypothalamic receptor sites. Salicylates can further uncouple oxidative phosphorylation in heatstroke and exacerbate coagulopathies. Acetaminophen may further stress hepatic function. The safety and efficacy of dantrolene are not established. Although aminocaproic acid impedes fibrinolysis, it may cause rhabdomyolysis and is not recommended in heatstroke.

DISPOSITION

Most patients with minor heat-emergency syndromes (including heat edema, heat syncope, and heat cramps) require only stabilization and treatment with outpatient follow-up. Although there are no decision rules to guide disposition choices in heat exhaustion, many of these patients have multiple predisposing factors and comorbidities that will require prolonged observation or hospital admission.

Essentially all patients with actual heatstroke require admission to a monitored setting, and most require intensive care. There are reports of very high survival rates of patients following prehospital immersion cooling without intensive care. Most or all of these patients appear to have had heat exhaustion. Many actual heatstroke patients also require prolonged tracheal intubation, invasive hemodynamic monitoring, and support for various degrees of multiorgan dysfunction syndrome. The prognosis worsens if the initial core temperature exceeds 42°C (107.6°F) or if there was a prolonged period during which the core temperature exceeded this level. Other features of a negative prognosis include acute renal failure, massively elevated liver enzymes, and significant hyperkalemia. As expected, the number of dysfunctional organ systems also correlates directly with mortality risk.

FURTHER READING

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