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14. ABSTRACT This chapter discusses the clinical manifestations, management, and prevention of heat-related illnesses. The spectrum of injury ranges from milder conditions such as heat cramps to fatal manifestations such as arrhythmias; it involves complications such as rhabdomyolysis and multiorgan dysfunction syndrome, and it may result in death from overwhelming cell necrosis caused by a lethal heat-shock exposure. Exertional heat stroke (EHS) is commonly characterized by development of mental status changes or collapse during physical activity in a warm environment. The severity of heat illness depends on the degree and duration of the elevation in core temperature (Tco). Heat stroke is an extreme medical emergency that can be fatal if it is not treated promptly with rapid cooling. To prevent and minimize complications and save lives, proper prevention, management, and clinical care are essential.					
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CHAPTER 11

Clinical Management of Heat-Related Illnesses

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This chapter discusses the clinical manifestations, management, and prevention of heat-related illnesses. The spectrum of injury ranges from milder conditions such as heat cramps to fatal manifestations such as arrhythmias; it involves complications such as rhabdomyolysis and multiorgan dysfunction syndrome, and it may result in death from overwhelming cell necrosis caused by a lethal heat-shock exposure. Exertional heat stroke (EHS) is commonly characterized by development of mental status changes or collapse during physical activity in a warm environment. The severity of heat illness depends on the degree and duration of the elevation in core temperature (T_{co}). Heat stroke is an extreme medical emergency that can be fatal if it is not treated promptly with rapid cooling. To prevent and minimize complications and save lives, proper prevention, management, and clinical care are essential.

Exertional Heat Illness

Dehydration and heat exposure can impair exercise performance and contribute to various illnesses. Exertional heat illnesses are comprised of minor and serious disorders. Minor heat and dehydration-related illnesses include heat cramps, erythromelalgia, and heat syncope. Heat cramps are characterized by intense muscle spasms, typically in the legs, arms, and abdomen. Heat cramps result from fluid and electrolyte deficits and occur most often in persons who have not been fully acclimated to a combination of intense muscular activity and environmental heat. Individuals who are susceptible to heat cramps are often believed to be profuse sweaters who sustain large sweat sodium losses.^{13,106} Heat syncope (fainting) is characterized by dizziness and weakness during or after prolonged standing or after rapidly standing up from a lying or sitting position during heat exposure. Heat syncope results from blood pooling in the cutaneous and skeletal vasculature, and it occurs most commonly in dehydrated and inactive persons who are not acclimated.⁹³ Erythromelalgia is characterized by pain and swelling in the feet and hands that is triggered by exposure to elevated temperatures.⁶⁴

Serious illnesses include exertional heat injury (EHI) and EHS. These illnesses have many overlapping diagnostic features; it has been suggested that they exist along a continuum on the severity scale.¹⁷ Heat exhaustion is characterized by inability to sustain cardiac output in the presence of moderate ($>38.5^{\circ}\text{C}$ [101°F]) to high ($>40^{\circ}\text{C}$ [104°F]) body temperatures, and is frequently accompanied by hot skin and dehydration. EHI is a moderate to severe illness characterized by injury to an organ (e.g., liver, kidneys, gut, muscle) and that usually (but not always) involves a high T_{co} of more than 40°C (104°F). EHS is a severe illness that is characterized by central nervous system dysfunction (e.g., confusion, disorientation, impaired judgment) and that is usually accompanied by a T_{co} of more than 40.5°C (105°F). EHI and EHS can be complicated by cardiac arrhythmia, liver damage, rhabdomyolysis, coagulopathy, fluid and electrolyte imbalances, and kidney failure. Rhabdomyolysis is most often observed with novel and strenuous overexertion. Clinical evidence suggests that dehydration increases the likelihood or severity of acute renal failure associated with rhabdomyolysis.^{19,91} Among U.S. soldiers who have been hospitalized for serious heat illness, 25% had rhabdomyolysis, and 13% had acute renal failure.²²

EHS is usually associated with prolonged exertion in a warm climate; however, in many instances, EHS occurs within the first 2 hours of exercise and not necessarily at high ambient

temperatures.^{17,37} This is because exertion and environmental heat stress during the 72 hours that precede such an event strongly influence the individual's susceptibility to heat illness.⁴⁰ Using a T_{co} of 40.5°C (104.9°F) as a critical temperature to initially diagnose EHS is arbitrary. Mental status changes in an individual who is performing exertion in the heat should be the defining characteristic of heat stroke unless the individual has sustained head trauma. At the stage of collapse, profuse sweating is still likely to be present unless heatstroke develops in an already anhidrotic individual. Dry skin may be evident either in situations in which the climate is very dry and sweat evaporates easily or when heatstroke coincides with a severe degree of dehydration.³⁶

Heat stroke is often categorized as either "classic" or "exertional," with the former primarily observed in elderly individuals or otherwise sick or compromised populations and the latter in apparently healthy and physically fit persons.

ON-SITE EMERGENCY MEDICAL TREATMENT

The early diagnosis of heat illness can be critical to therapeutic success. Early warning signs include flushed face, hyperventilation, headache, dizziness, nausea, tingling arms, piloerection, chilliness, incoordination, and confusion.⁷⁴ If the patient is alert and has no mental status changes, he or she can rest in the shade or indoors, and oral rehydration can be instituted with cold water or an electrolyte-replacement beverage. The concentration of carbohydrates in such a beverage should not exceed 6%; otherwise, gastric emptying and fluid absorption by the intestines may be delayed. Responders should target an intake of 1 to 2 L (0.9 to 1.8 qt) over 1 hour. If the patient does not improve or in fact worsens, he or she should be evaluated by a medical provider. All persons with suspected heat injuries should be observed to ensure that decompensation does not occur. The victim should continue to rest and drink over the next 24 hours. As a general rule, for every pound of weight lost by sweating, 0.5 qt (2 cups or 500 mL) of fluid should be consumed. It may require 36 hours to completely restore lost electrolytes and fluid volume to all body compartments via oral intake. After the acute episode, a medical provider should determine any possible host risk factors for heat illness and review with the victim the signs of heat illness and preventive measures to consider.

Any athlete who is performing exercise in warm weather and who develops mental status changes in the absence of trauma should be treated as an EHS victim until proved otherwise.³⁶ EHS is a medical emergency. Rapid reduction of elevated T_{co} is the cornerstone of EHS management; the duration of hyperthermia may be the primary determinant of outcome.^{59,100} Cooling should not be delayed so that a temperature measurement can be obtained. Cooling measures should only be minimally delayed for vital resuscitation measures. Nevertheless, it is important to follow the ABCs (airway, breathing, and circulation) of stabilization while cooling efforts are initiated; see Box 11-1 for basic first aid information. Before 1950, the mortality rate with EHS was 40% to 75%.^{6,35} Long-term survival is directly related to rapid institution of resuscitative measures.⁴⁹

In the field, the sick individual should be placed in the shade, and any restrictive clothing should be removed. There are multiple ways to cool victims in the field, with cold-water immersion (CWI) being the most effective modality.^{24,86} In a remote setting, this can be accomplished by using a small children's pool filled

BOX 11-1 Basic First Aid for Heat Illnesses

1. Place the patient in the shade.
2. Assess airway, breathing, and circulation.
3. Initiate cardiopulmonary resuscitation if the patient is pulseless or apneic.
4. Remove any restrictive clothing.
5. Initiate rapid cooling measures.
6. Activate emergency medical services.
7. Measure the patient's rectal temperature to confirm the diagnosis
8. Evacuate the patient to the nearest medical facility via emergency medical services.

with iced water. The victim should be submerged up to the shoulders and kept under immediate hands-on supervision at all times. Another expedient method in the field is to keep bed sheets soaked in a cooler full of iced water; the victim can then be wrapped in the cold sheets. Particular care should be given to covering the head and to resubmerging the sheets every few minutes to recool them.⁷⁹ Ice packs can be applied to the groin, axillae, sides of the neck, and head to augment iced-sheet cooling. Cooling should continue until emergency medical services providers arrive. Nonmedical first responders should not attempt to evacuate heat stroke patients themselves, because this may distract from cooling efforts. If CWI or iced sheets are not available, the victim should be kept wet by applying large quantities (20 to 30 L [5.3 to 7.9 gal]) of tap water or water from any source, and the victim's body should be constantly fanned. Cooling blankets are generally ineffective as a single modality for inducing the rapid lowering of body temperature required for treating heatstroke.

EMERGENCY MEDICAL SERVICES TREATMENT

During evacuation, CWI is often not a viable method for treatment. Iced sheets and ice packs can be easily used en route during transport. Many EMS vehicles now carry refrigerated intravenous (IV) fluid to initiate induction of therapeutic hypothermia in cardiovascular emergencies. When used, chilled IV fluid (4° C [39° F]) should be peripherally administered.⁶³ Vascular access should be established without delay by inserting a 12- or 14-gauge IV catheter. Administration of normal saline or lactated Ringer's solution should be started. Recommendations vary regarding administration rate of fluids. Some clinicians advise a rate of 1200 mL (1.26 qt) over 4 hours,⁷⁸ whereas others encourage a 2-L (2.11-qt) bolus over the first hour and an additional liter of fluid per hour for the next 3 hours.⁹⁸ Patients should be placed on a cardiac monitor. Administration of supplemental oxygen may help to meet the victim's increased metabolic demands, and it may also be used to treat hypoxia that is commonly associated with aspiration, pulmonary hemorrhage, pulmonary infarction, pneumonitis, or pulmonary edema.^{34,67} A blood glucose determination should be performed, and adults with blood sugar level less than 60 mg/dL should be treated with 1 ampule of 50% IV dextrose solution. Children should be treated with 2 to 4 cc/kg of 25% IV dextrose solution.

The use of antipyretics is not effective and may potentially be harmful to heatstroke victims. Aspirin and acetaminophen lower T_{co} by normalizing the elevated hypothalamic set point that is caused by pyrogens; in heatstroke, the set point is normal, with T_{co} elevation reflecting a failure of normal cooling mechanisms. Furthermore, acetaminophen may induce additional hepatic damage, and administration of aspirin may aggravate bleeding tendencies. Alcohol sponge baths are inappropriate under any circumstances, because transcutaneous absorption of alcohol may lead to poisoning and coma.

In a comatose victim, airway control should be established by inserting a cuffed endotracheal tube. Positive-pressure ventilation is indicated if hypoxia persists despite supplemental oxygen administration.

The victim's altered mental status may adversely affect the ability of emergency department personnel to obtain a detailed history of precipitating events. Lack of such information may also delay diagnosis. Emergency medical transport personnel should attempt to obtain this history before evacuating the victim and should communicate the information to medical staff. Of particular importance is the duration—and, when available, the maximum degree—of hyperthermia.

HOSPITAL EMERGENCY MEDICAL TREATMENT

Patients with suspected heat stroke should be placed in a large treatment room to accommodate the needed number of staff. Patients are often combative and disoriented before reestablishing their baseline mental status. Aggressive cooling measures should continue until mental status returns to normal and T_{co} is 39° C (102° F).²⁴ After discontinuation of cooling, T_{co} should be monitored every 5 minutes to ensure that it does not increase.

The T_{co} reported in the field for heatstroke victims may be significantly higher (e.g., 41.1° C [106.9° F]), than those documented in the hospital emergency department (e.g., 37.8° C [100° F]), because T_{co} may fall during transport to the hospital.⁹⁹ Documenting only a mild elevation in T_{co} on arrival does not exclude the diagnosis of heatstroke. Central nervous system (CNS) disturbances (i.e., coma, convulsions, confusion, or agitation) that accompany hyperthermia may also result from CNS infections, sepsis, or other disease processes. Other diagnoses should be considered when the patient does not regain normal mental status when the T_{co} is normalized in less than 30 minutes. When T_{co} remains elevated for a longer time, there is a decreased likelihood that mental status will normalize with euthermia.¹⁷

T_{co} can be measured at several anatomic sites, but oral, tympanic, esophageal, and rectal temperatures show regional variations as a result of differences in tissue metabolic activity, local blood supply, and temperature gradients between neighboring tissues. During exercise, active skeletal muscle temperature differs dramatically from that of other areas of the body that are not directly involved in the activity. Oral temperature is considered to be similar to blood temperature as a result of the rich blood supply of the tongue, but it is also influenced by hyperventilation and drinking fluids. Rectal temperature is a highly reliable indicator of body temperature, but it has a slower response rate and gives slightly higher readings than do other sites in the body.

The comparison of oral and rectal temperature values in heatstressed underground miners showed a difference of approximately 1° C (2° F), with oral temperatures underestimating rectal values.¹⁰⁸ Tympanic temperature responds more rapidly to cooling or heating than does rectal temperature, but it is influenced by changes in the skin temperature of the head and neck.^{44,68} The ear should be insulated from the environment to prevent cool ambient temperatures (<30° C [86° F]) from affecting this measurement. Esophageal temperature is the most accurate and responsive to changes in blood temperature, but its instrumentation is impractical in severely injured or unresponsive patients.

If airway control was not previously established and if the patient is still unconscious, a cuffed endotracheal tube should be inserted to protect against aspiration of oral secretions. Supplemental oxygen—and, when hypoxia (Pao_2 <55 mm Hg) or hypotension is present, positive-pressure ventilation—should be provided. Overly vigorous fluid resuscitation may precipitate pulmonary edema, so careful monitoring is indicated. Ideally, 1 to 2 L (1.05 to 2.11 qt) of fluid should be administered during the first hour after collapse, and additional fluids should be administered until satisfactory urine output (0.5 cc/kg/hr in an adult and 1.0 cc/kg/hr in a child) is established.³⁸ Most heatstroke victims arrive with a high cardiac index, low peripheral vascular resistance, and mild right-sided heart failure with elevated central venous pressure. Only moderate fluid replacement is indicated if effective cooling results in vasoconstriction and increased blood pressure. Providers should consider noninvasive intravascular volume monitoring or the minimally invasive monitoring of systolic volume variation and pulse pressure variation. If these methods are not adequate, a Swan-Ganz pulmonary artery catheter may be

necessary to assess appropriate fluid supplementation. Some victims have a low cardiac index, hypotension, and elevated central venous pressure. These persons have been successfully treated with an isoproterenol drip (1 mg/min).⁷⁸ Patients with a low cardiac index, low central venous pressure, hypotension, and low pulmonary capillary wedge pressure should receive fluid. Unless the patient has rhabdomyolysis, aggressive fluid hydration is seldom required after initial treatment.

Cardiac monitoring should be maintained during at least the first 24 hours of hospitalization. Arrhythmia is most likely to occur during hyperthermia, but it may also occur as a result of electrolyte abnormalities. The use of norepinephrine and other α -adrenergic drugs should be avoided because they cause vasoconstriction, thereby reducing heat exchange through the skin. Anticholinergic drugs that inhibit sweating (e.g., atropine) should also be avoided.

Cooling techniques are ineffective when the victim suffers seizures that increase storage of body heat; therefore, convulsions should be controlled. Intravenous benzodiazepines are preferred for their efficacy and renal clearance. Initial dosing is either 4 to 8 mg of IV lorazepam or 10 mg of IV diazepam. If seizures persist for more than 10 minutes after the first dose, an additional 4 mg of lorazepam or 10 mg of diazepam should be administered.

As a result of drastic cooling, skin temperature may decrease enough to cause shivering. Administration of 12.5 mg of meperidine via slow IV push¹⁰³ or of 5 mg of diazepam is effective to suppress shivering and to prevent an additional rise in T_{co} from metabolic heat production. If CWI is used, the increase in metabolic rate as a result of shivering will be more than offset by the high rate of heat transfer. Therefore the presence of shivering should not be a cause for concern when this method of cooling is used.^{24,83}

Severe muscle cramping may be caused by electrolyte imbalances. Magnesium levels should be obtained. If magnesium levels are low, consideration may be given to the use of 50% IV magnesium sulfate (4 g in 250 mL of 5% dextrose injection at a rate that does not exceed 3 mL per minute).^{14,15}

A Foley catheter should be placed to monitor urine output. Renal damage from myoglobinuria and hyperuricemia can be prevented by promoting renal blood flow by administering IV mannitol (0.25 mg/kg) or furosemide (1 mg/kg).⁹⁸ If creatine phosphokinase (CPK) levels exceed 100,000 international units, alkalinize the urine of patients with exertional rhabdomyolysis; there is no advantage to alkalinization when levels are lower. Hemodialysis should be reconsidered if anuria, oliguria (<0.5 mL/kg of urine per hr for >6 hr), uremia, or hyperkalemia develops. Cooling and hydration usually correct acid-base abnormalities; however, serum electrolytes should be monitored and appropriate modifications of IV fluids made. Glucose should be monitored repeatedly, because either hypoglycemia or hyperglycemia may occur after EHS.⁹⁵ Oral and gastric secretions are evacuated via a nasogastric tube that is connected to continuous low suction. Although antacids, proton pump inhibitors, and histamine-2 blockers have been used to prevent gastrointestinal bleeding, no studies to date demonstrate their efficacy for heatstroke victims.

Induced Hypothermia

Induced hypothermia is increasingly being used for many neurologic and cardiovascular emergencies, including acute stroke, neonatal hypoxic-ischemic encephalopathy, and after cardiac arrest.^{9,50,76,94} This therapeutic modality has not been evaluated for effectiveness in individuals with EHS, but may have a role in cooling severe refractory cases of EHS. There may be a role for a period of induced hypothermia after severe EHS.

Dantrolene

No drug has been found to have a significant effect for reducing T_{co} . Antipyretics are ineffective, because the thermoregulatory set point is not affected in heatstroke. Furthermore, antipyretics might be harmful, because they cannot be readily metabolized in the heat-affected liver. However, dantrolene has been used quite successfully for the treatment of several hypercatabolic syndromes, such as malignant hyperthermia, neuroleptic malignant syndrome, and other conditions that are characterized by muscular rigidity or spasticity.^{107,114} Dantrolene stabilizes the

calcium (Ca^{2+})-release channel in muscle cells, thereby reducing the amount of Ca^{2+} released from cellular calcium stores. This lowers intracellular Ca^{2+} concentrations, muscle metabolic activity, muscle tone, and thus heat production.^{27,75} In some studies, dantrolene was claimed to be effective for the treatment of heatstroke, whereas in others it improved neither the rate of cooling nor survival.^{25,31,66,109} In six patients with rhabdomyolysis, intramuscular Ca^{2+} concentrations were 11 times higher than in controls, and dantrolene successfully lowered this elevated Ca^{2+} .⁶⁵ Collectively, the limited data available are at best inconsistent. Despite growing evidence for a possible benefit of dantrolene treatment in patients with heatstroke, justification for its routine use in such cases is not proved, although future clinical trials may change this assessment.

Moran and colleagues⁷¹ studied dantrolene in a hyperthermic rat model, and found it to be effective as a prophylactic agent in sedentary animals only. Dantrolene induced more rapid cooling by depressing Ca^{2+} entry into the sarcoplasm; this led to relaxation of peripheral blood vessels with attenuated production of metabolic heat. Dantrolene may also be effective in treating heatstroke by increasing the cooling rate. However, in other animal models, dantrolene was not superior to conventional cooling methods.¹¹⁷ As such, dantrolene is not recommended.

CLINICAL MANIFESTATIONS

Clinical manifestations of heatstroke vary, depending on whether the victim suffers from classic heatstroke, which is a common disorder of older adults during heat waves and occurs in the form of epidemics, or EHS,¹ which occurs when excess heat generated by muscular exercise exceeds the body's ability to dissipate it (Table 11-1). Some overlap in presentation may occur; treatment with a medication (e.g., antihypertensive or antipsychotic) that places an older adult at risk for classic heatstroke also places an exercising individual at risk for EHS. The clinical picture of heatstroke usually follows a distinct pattern of events

TABLE 11-1 Comparison of Classic and Exertional Heatstroke

Characteristics	Classic	Exertional
Age group	Young children and older adults	Men between the ages of 15 and 45 yr
Health status	Chronically ill	Healthy
Concurrent activity	Sedentary	Strenuous exercise
Drug use	Diuretics, antidepressants, antihypertensives, anticholinergics, and antipsychotics	Usually none
Sweating	May be absent	Usually present
Lactic acidosis	Usually absent; poor prognosis if present	Common
Hyperkalemia	Usually absent	Often present
Hypocalcemia	Uncommon	Frequent
Hypoglycemia	Uncommon	Common
Creatine phosphokinase	Mildly elevated	Markedly elevated
Rhabdomyolysis	Unusual	Frequently severe
Hyperuricemia	Mild	Severe
Acute renal failure	<5% of patients	25-30% of patients
Disseminated intravascular coagulation	Mild	Marked; poor prognosis
Mechanism	Poor dissipation of environmental heat	Excessive endogenous heat production and overwhelming heat-loss mechanisms

Modified from Knochel JP, Reed G: *Disorders of heat regulation*. In Kleeman CR, Maxwell MH, Narin RG, editors: *Clinical disorders of fluid and electrolyte metabolism*. New York, 1987, McGraw-Hill.

with three phases: (1) acute; (2) hematologic or enzymatic; and (3) late.³⁸

Acute Phase

The acute phase of heatstroke is characterized by CNS manifestations. Because brain function is very sensitive to hyperthermia, this phase is present in all heatstroke patients. Early signs of CNS dysfunction are typically cerebellar and include ataxia, poor coordination, and dysarthria.¹¹⁶ Advanced signs of CNS depression include irritability, aggressiveness, stupor, delirium, and coma.^{2,21,102} Mental status changes usually resolve after return to a normal T_{co} . After a return to normothermia, persistence of coma is a poor prognostic sign.^{57,102} Other symptoms include fecal incontinence, flaccidity, and hemiplegia. Cerebellar symptoms may persist beyond the acute phase.^{69,102,116}

Other common disturbances during the acute phase occur in the gastrointestinal and respiratory systems. Gastrointestinal dysfunction, including diarrhea and vomiting, often occurs. However, the latter may reflect translocation of toxic gram-negative bacterial lipopolysaccharide from the lumen of the intestines because of poor splanchnic perfusion as a result of hypotension caused by increased skin blood flow and from CNS impairment.^{18,41,102} Hyperventilation and elevation of T_{co} primarily lead to respiratory alkalosis, which in EHS may be masked by metabolic acidosis as a result of increased glycolysis and hyperlactacidemia.^{26,74} Hypoxemia may be present in patients with respiratory complications.^{28,74,105} It should also be noted that oxygen consumption is elevated during hyperthermia, with a 10% to 13% increase for every °C above euthermia.³²

EHS shares many common findings with systemic inflammatory response syndrome (SIRS).^{17,97} Endotoxemia, hyperthermia, and other risk factors (e.g., preexisting infection) and stressors associated with EHS can trigger this exaggerated inflammatory response. Patients should be assessed for SIRS after admission with the use of the following criteria:¹⁶ (1) body temperature of less than 36° C (98.6° F) or of more than 38° C (100.4° F); a heart rate of more than 90 beats per minute, tachypnea, or an arterial partial pressure of carbon dioxide of less than 4.3 kPa (32 mm Hg); and a white blood cell count of less than 4000 cells/mm³ (4×10^9 cells/L) or of more than 12,000 cells/mm³ (12×10^9 cells/L) or the presence of more than 10% immature neutrophils. When two or more of these criteria are met, SIRS can be diagnosed. The presence of systemic inflammatory response markers during the acute phase predicts the severity of subsequent phases.

Hematologic and Enzymatic Phase

Hematologic and enzymatic disorders peak 24 to 48 hours after collapse. In the hematologic and enzymatic phase of EHS, hematologic, enzymatic, and other blood parameters are altered. In humans and experimental animals, hyperthermia results in leukocyte activation⁴⁶ and in changes in lymphocyte subpopulations, both in absolute numbers and in percentages.¹ Leukocytes may range from 20 to 30 $\times 10^3$ /mm³ or higher.^{10,51} In severe cases, leukocyte activation is associated with the systemic activation of coagulation cascades.⁵⁵ In one study, all fatal cases of EHS involved disturbances in the blood coagulation system.^{10,101} Prothrombin time, partial thromboplastin time, and the level of fibrin split products increased with a fall in thrombocytes.³⁸ Clotting dysfunction peaked 18 to 36 hours after the acute phase of heatstroke; 2 to 3 days after heatstroke, prothrombin levels fell to 17% to 45% of normal. Depending on the severity of heatstroke, thrombocyte values ranged between 110 $\times 10^3$ /mm³ and 0.^{100,101} This systemic inflammatory response state resembles gram-negative bacterial sepsis, and it appears that lipopolysaccharide (a cell-wall component of gram-negative bacteria) participates in the pathophysiology of EHS.⁴³

Enzymes

One of the prominent and almost pathognomonic characteristics of EHS is the appearance of exceptionally high levels of certain cellular enzymes, which implies cell damage or death. Most patients with EHS show an elevation of serum CPK activity and myoglobinuria, which suggests damage to skeletal muscle.³⁷ CPK values in the range of 10³ to 10⁴ international units were

commonly found, with peak values occurring 24 to 48 hours after collapse.^{30,96} At a T_{co} of 41.8° to 42.2° C (107.24° to 107.96° F), aspartate aminotransferase and alanine aminotransferase levels rose by factors of 25 and 8, respectively, and bilirubin levels approximately doubled to 1.56 mg/dL.⁸²

These rises in enzyme levels are related to tissue damage, which in turn depends on both T_{co} and its rates of rise and duration.⁷³ CPK was the most sensitive to increases in T_{co} , and this was followed by lactate dehydrogenase, which is an index of generalized tissue damage. CPK levels in EHI and EHS typically peak at 24 to 48 hours. Rising values after this point should alert the clinician to the possibility of an occult compartment syndrome. It is not uncommon for a victim of EHI to complain of lower-extremity pain that declares itself as a compartment syndrome. During the 1994 Hajj, 26 heatstroke victims admitted to a heatstroke treatment unit had elevated levels of CPK, aspartate aminotransferase, alanine aminotransferase, and lactate dehydrogenase; these levels remained high after 24 hours. Those who died had higher enzyme levels than did the survivors. Lactate dehydrogenase concentration was useful for distinguishing between those who died and those who had a rapid recovery. The enzymes were better prognostic indicators than were T_{co} , anion gap, and serum potassium level.

Late Phase

The late phase of heatstroke manifests 3 to 5 days after collapse, and is characterized by disturbances in renal and hepatic functions. These abnormalities are consistent with multiorgan dysfunction syndrome as a result of SIRS.

Acute renal failure is a common complication of severe cases, and occurs in approximately 25% to 30% of patients with EHS patients.^{60,67,100} Oliguria and anuria are characteristic features. During this phase, urine has been described as being like machine oil, with a high specific gravity.^{81,84,92,100} Usually present in the urine are red and white cells, hyaline and granular casts, and mild to moderate proteinuria.⁹² The etiology involves multiple causes,⁸¹ but a major one is reduced renal blood flow caused by heat-induced hypotension, hypohydration, and peripheral vasodilation. In addition, direct thermal injury may also lead to widespread renal tissue damage.⁹² Myoglobinuria and elevated blood viscosity that result from disseminated intravascular coagulation may further contribute to acute oliguric renal failure.^{84,92,104,111}

EHS is usually manifested by increased serum levels of liver enzymes, but acute liver failure has also been reported.^{115,39} High bilirubin levels, which may last for several days, reflect hepatic dysfunction and hemolysis. In most cases of EHS, liver injury is usually asymptomatic and exhibits reversible elevation in plasma aminotransferase levels.⁴⁸ Acute liver failure is documented in 5% of patients with EHS.⁶¹ Hypophosphatemia (<0.5 mmol/L) at the time of admission may predict occurrence of acute liver failure.³⁹ Despite limited experience and the observation that EHS patients with extensive liver damage may recover spontaneously, orthotopic liver transplantation had been suggested as a potential treatment.^{12,47,89} Among 16 reported cases of EHS-induced liver failure,⁴⁵ three patients underwent liver transplantation. In the conservatively managed group, eight patients recovered spontaneously, and five died. Concomitantly, all three patients who received transplantation died. Hadad and co-workers⁴⁵ concluded that, because of the poor and limited results of liver transplantation after heatstroke, the interpretation of prognostic criteria is crucial before listing a patient for such surgery.

SEQUELAE AND AFTERCARE

The combination of the rapid reduction of T_{co} , control of seizures, proper rehydration, and prompt evacuation to an emergency medical facility results in a 90% to 95% survival rate in heatstroke victims, with morbidity directly related to the duration of hyperthermia.^{17,97} A poor prognosis is associated with T_{co} of more than 41° C (105.8° F), prolonged duration of hyperthermia, hyperkalemia, acute renal failure, and elevated serum levels of liver enzymes. Therefore misdiagnosis, early inefficient treatment, and delay in evacuation are the major causes of clinical deterioration. Full recovery without evidence of neurologic impairment has been achieved even after coma of 24 hours' duration and

subsequent seizures.¹⁰¹ Persistence of coma after return to normothermia is a poor prognostic sign.¹⁰² Red blood cell apoptosis (i.e., cell blebbing, asymmetry, and shrinkage) on early peripheral blood smears is a very poor prognostic sign and may indicate extensive cellular necrosis. Neurologic deficits may persist, but usually only last for a limited period of 12 to 24 months and only rarely for longer.

CNS dysfunction becomes increasingly severe with prolonged duration of hyperthermia and associated circulatory failure. Nevertheless, coma that persists for up to 24 hours, even with subsequent seizures, is usually followed by complete recovery without evidence of mental or neurologic impairment.^{2,88} However, chronic disability may prevail for several weeks or months in the forms of cerebellar deficits, hemiparesis, aphasia, and mental deficiency.^{2,60,88} Only in exceptional cases, when coma persisted for more than 24 hours, did mental and neurologic impairment become chronic and prevail for years. However, in one study of classic heatstroke, 78% of patients had minimal to severe neurologic impairment, such as ataxia or dysarthria.³⁰ Long-term EHS victims may have increased mortality from heart, liver, and kidney disease.¹¹³

PREVENTION

Prevention of heat illness relies on an awareness of host risk factors, altering behavior and physical activity to match these risk factors and environmental conditions, and a requirement for appropriate hydration during physical exercise in the heat. More aggressive educational activity that explains heat illness and its prevention to the public is to be strongly promoted. Primary care physicians should incorporate this information into the anticipatory guidance of routine health assessment. Despite a wealth of medical literature about heat injury, some athletic coaches continue to use physical or psychological methods to force athletes to compete or train under intolerably hot conditions. This practice should be viewed as irresponsible, dangerous, and possibly criminally negligent.

The importance of recognizing milder forms of heat illness cannot be overstated. Any time heat injuries occur, coaches and trainers should reassess all athletes and determine what other measures can be implemented to prevent more serious injuries from occurring.

Awareness of Host Risk Factors

Shapiro and Moran⁹⁶ studied 82 cases of EHS in Israeli soldiers and concluded that at least one factor that predisposes an individual to heatstroke (e.g., diarrhea, lack of acclimatization, poor fitness) was associated with each case. Correcting those individual risk factors should lead to strategies that can prevent heatstroke. Any underlying condition that causes dehydration or increased heat production or that causes decreased dissipation of heat interferes with normal thermoregulatory mechanisms and predisposes an individual to heat injury. Older individuals are less tolerant to EHI than younger persons, and they are more susceptible to classic heatstroke because of decreased secretory ability of their sweat glands and decreased ability of their cardiovascular systems to increase blood flow to the skin. When healthy young adults exercise strenuously in the heat, EHS may occur despite the absence of host risk factors.

Elite and professional athletes, the general public, and the military have widely used ergogenic aids (e.g., the herb ephedra [*ma buang*]) that contain ephedrine to improve performance and for weight loss. Because ephedra increases metabolic rate, it has caused numerous cases of heat illness and deaths worldwide, and it has been banned. Because there are no clear ergogenic benefits to the use of ephedra alone, use of ephedra-containing substances should be discouraged.⁸⁰

The ratio of basal metabolic rate to surface area is higher in children than in adults. As a result, a child's skin temperature is higher for any given T_{co} . Although the secretory rates of sweat glands are lower in children, children have greater numbers of active sweat glands per area of skin than adults and overall greater sweat rates per unit area.⁵⁴ Any reduction in the rate of sweating puts children especially at risk. The primary mechanism for heat stroke in young children is hot vehicle entrapment.

Between 1998 and 2010, 462 children died from heat stroke as a result of vehicular hyperthermia.

The primary means of heat dissipation is production and evaporation of sweat. Any condition that reduces this process places the individual at risk for thermal injury. Poor physical conditioning, fatigue, sleep deprivation, cardiovascular disease, and lack of acclimation all limit the cardiovascular response to heat stress.^{40,56} Obesity places an individual at risk as a result of reduced cardiac output, the increased energy cost of moving extra mass, increased thermal insulation, and altered distribution of heat-activated sweat glands.⁷² Older adults and younger individuals show decreased efficiency of thermoregulatory functions and increased risk for heat injury.

Several congenital or acquired skin abnormalities affect sweat production and evaporation. Ectodermal dysplasia is the most common form of congenital anhidrosis. Widespread psoriasis, poison ivy, sunburn, scleroderma, miliaria rubra (i.e., "prickly heat," which is caused by the plugging of sweat ducts with keratin), deep burns, and prior skin grafting may also limit sweat production.

Dehydration affects both central thermoregulation and sweating. A mere 2% decrease in body mass through fluid loss produces an increase in heart rate, increase in T_{co} , and decrease in plasma volume. In an otherwise healthy adult, gastrointestinal infection with vomiting and diarrhea may cause sufficient dehydration to place the individual at risk for EHS.

Chronic conditions that may contribute to heat illness include diabetes mellitus, diabetes insipidus, spinal cord injury, eating disorders (especially bulimia), and mental retardation. Alcoholism and illicit drug use are among the 10 major risk factors for heatstroke in the general population.⁵⁸ An important effect of alcohol consumption is inhibition of antidiuretic hormone secretion, which leads to relative dehydration. Autonomic dysfunction, which is present with many chronic diseases, impairs thermoregulation.⁵²

Despite evidence that hypohydration limits physical performance, voluntary dehydration continues to be routine in certain athletic arenas.^{5,7,20,110} Wrestlers, jockeys, boxers, and bodybuilders commonly lose 3% to 5% of their body mass 1 to 2 days before competition. In addition to restricting fluid and food, they use other pathogenic weight-control measures, such as self-induced vomiting, laxatives, diuretics, and exposure to heat (e.g., saunas, hot tubs, "sauna suits"). Athletes who are undergoing rapid dehydration are at risk not only for heat injury but also for other serious medical conditions, such as pulmonary embolism.²⁹

Box 11-2 highlights common medications that interfere with thermoregulation. Special attention should be paid to the role of antihistamines in reducing sweating. This class of medications is commonly obtained over the counter, so the general population should be warned about the dangers of exercising in the heat when they are taking antihistamines.

Although it has been widely believed that sustaining an episode of heatstroke predisposes the individual to future heat injury, this has been refuted in a recent study of heatstroke victims.⁸ Ten heatstroke patients were tested for their ability to acclimate to heat;

BOX 11-2 Drugs That Interfere With Thermoregulation

Drugs That Increase Heat Production

- Thyroid hormone
- Amphetamines
- Tricyclic antidepressants
- Lysergic acid diethylamide

Drugs That Decrease Thirst

- Haloperidol

Drugs That Decrease Sweating

- Antihistamines
- Anticholinergics
- Phenothiazines
- Benztropine mesylate

Data from references 12, 31, 50, 66, 105, and 107.

by definition, the ability to acclimate to heat indicates heat tolerance. Nine of the patients demonstrated heat tolerance within 3 months after the heatstroke episode; the remaining patient acclimated to heat one year after his heat injury. In no case was heat intolerance permanent. Although individuals may show transient heat intolerance after thermal injury, evidence for permanent susceptibility to thermal injury is lacking.

ADAPTATION TO ENVIRONMENTAL CONDITIONS

Appropriate adaptation to hot environmental conditions encompasses many forms of behavior, including modifying clothing, the degree of physical activity, searching for shade, the anticipatory enhancement of physical conditioning, acclimation to heat stress, and paying attention to the level of hydration.

Clothing

Different regions of the body are not equivalent with regard to sweat production.⁵³ The face and the scalp account for 50% of total sweat production, whereas the lower extremities contribute only 25%. When exercising under conditions of high heat load, maximal sweat evaporation is facilitated by maximal skin exposure. Clothing should be lightweight and absorbent. Although significant improvement has been made in the fabrication of athletic uniforms, the uniforms and protective gear required by certain branches of the military and public safety officers continue to add to the risk of heat injury. Developing protective clothing that permits for more effective heat dissipation is indicated. Uniforms should be modified to decrease the amount of extra protective equipment and head gear needed as much as is safely possible during the first week of training and during times of high heat stress conditions.

Activity

Behavioral actions can effectively minimize the occurrence of classic heatstroke. Lack of residential air conditioning places indigent persons at risk during heat waves. By sitting in a cool or tepid bath periodically throughout the day, the individual can decrease heat stress and thereby prevent heat injury. The more than 10,000 deaths during the 2003 heat wave in Europe could have been reduced by simple announcements by public health officials of this preventive measure. This type of “heat dumping” activity can also include taking cool showers instead of warm showers. In addition, the forearms and hands can be immersed into water that has been cooled to 10° to 20° C (50° to 68° F) for a period of 10 minutes. This action will achieve a reduction in T_{co} of 0.7° C (1.3° F) and provide the athlete with sustained capability to train in the heat.⁴²

In addition to forearm and hand immersion in cool or cold water, the concept of cooling the palm by various devices, some of which add vacuum pressure to the palm in addition to cooling, has recently become popular. A comprehensive review²³ of cooling rates of various cooling modalities has shown that this methodology is no more effective in lowering body core temperature than limb immersion in tap water (15° C [59° F]). Recent research on these devices has shown that the addition of negative pressure with cooling did not enhance any cooling effect.⁶² In addition, these devices have been shown to be ineffective in slowing the development of hyperthermia when used between exercise bouts⁴ and in the improvement of high-intensity, intermittent exercise.¹¹² Cold or ice water has been reported to have a cooling power of 5 to 8 times greater than hand/palm cooling devices.²³ Given the low cooling power of these devices, their use in a field or athletic setting, especially for treatment of heat injury or illness, should be questioned. This is also true when viewed in terms of cost vs. limb immersion modalities. Regarding use in a wilderness setting, these devices have additional drawbacks including the need for electrical power via batteries and the added weight of transport.

Athletes should be placed in the shade whenever possible during periods of rest and instruction. If shade is not available in areas where warm weather training is routinely conducted, consideration should be given to constructing overhead shelters. If latrines are not easily accessed at training areas, consideration

TABLE 11-2 Determination of Wet Bulb Globe Temperature Heat Index

Temperature (T, in ° F)	Factor	Example
Wet bulb T	×0.7	78 × 0.7 = 54.6
Dry bulb T	×0.1	80 × 0.1 = 8.0
Black globe T	×0.2	100 × 0.2 = 20.0
Heat index		82.6

Wet bulb reflects humidity, dry bulb reflects ambient air temperature, and black globe reflects radiant heat load; the heat index is the sum of the three. Alternative equation: Wet bulb globe temperature = $(0.567 T_{db}) + (0.393 P_a) + 3.94$, where T_{db} is dry bulb temperature and P_a is water vapor pressure.

should be given to placing portable latrines nearby to prevent voluntary fluid restriction. The authors recommend spacing runners widely apart during group runs to allow for optimal heat dissipation.

Modification of physical activity should not be based solely on any individual parameter of ambient temperature (T_{amb}), relative humidity, or solar radiation, because all of these contribute to heat load. The wet bulb globe temperature (WBGT) is an index of heat stress that incorporates all three factors. This value may be calculated (Table 11-2), or it may be obtained directly from portable digital heat-stress monitors that measure all three parameters simultaneously to compute the WBGT. When heat-stress monitors are used, care should be taken to ensure that they are calibrated yearly and that they are not left out in the heat for long periods of time without use. Care should also be taken to ensure that the device measures radiant heat, humidity, air movement, and shaded temperature to calculate WBGT. Devices that measure the heat stress index, relative humidity, and wind speed should not be used to estimate WBGT. Current recommendations from the American College of Sports Medicine for preventing exertional heat illness during workouts and competition are based on the WBGT.³ Most heat injuries occur during cooler WBGT periods as a result of cumulative heat exposure from preceding days. Some clinicians have proposed that heat-warning systems would base their warnings on cumulative heat stress rather than solely on the current WBGT.¹¹³ Other clinicians have suggested the use of syndromic surveillance to help alert the public about periods of high heat stress.¹¹

Table 11-3 presents a suggested modification of sports activity that is also based on the WBGT. Although American College of Sports Medicine guidelines for the summer indicate that vigorous physical activity should be scheduled in the morning or evening, individuals should be cautioned that the highest humidity of the

TABLE 11-3 Modification of Sports Activity on the Basis of Wet Bulb Globe Temperature

Index	Limitation
<10° C (50° F)	There is a low risk for hyperthermia but a possible risk for hypothermia.
<18.3° C (65° F)	There is a low risk for heat illness.
18.3-22.8° C (65-73° F)	There is a moderate risk toward the end of the workout.
22.8-27.8° C (73-82° F)	Those at high risk for heat injury should not continue to train; all athletes should practice in shorts and T-shirts during the first week of training.
27.8-28.9° C (82-84° F)	Care should be taken by all athletes to maintain adequate hydration.
28.9-31.1° C (85-88° F)	Unacclimated persons should stop training; all outdoor drills in heavy uniforms should be canceled.
31.1-32.2° C (88-90° F)	Acclimated athletes should exercise caution and continue workouts only at a reduced intensity; they should wear light clothing only.
≥32.2° C (90° F)	Stop all training.

day is usually during early morning. In 1999, Montain and co-workers⁷⁰ updated the fluid replacement guidelines for warm-weather training (see Chapter 70, Table 70-5). It is important to note that compliance with these recommendations does not remove all risk of heat injury. The development of another index of heat stress that provides a better basis for the prevention of EHS is indicated.

Rav-Acha and colleagues⁸⁵ assembled a case series of six fatal cases of EHS in the Israeli Defense Forces and examined the circumstances that led to the deaths. A significant association between the accumulation of predisposing factors and EHS totality was found. In almost all of the fatal cases, seven predisposing factors were noticed: (1) low physical fitness; (2) sleep deprivation; (3) high heat load; (4) high solar radiation; (5) physical exercise unmatched to physical fitness; (6) absence of proper medical triage; and (7) training during the hottest hours. These fatality factors primarily concerned organizational training regulations and not individual factors, which emphasizes the importance of proper guidelines and safety measures in a warm climate—rather than individual characteristics—for preventing EHS fatalities. It follows that a combination of predisposing factors that were already found to impair heat tolerance⁴⁰ is a strong predictor of a grave prognosis. Dehydration was found in only two of the six cases reported.

Conditioning

The contribution of cardiovascular conditioning to thermoregulation is discussed in Chapter 4. Ideally, an individual should train under temperate or thermoneutral conditions before exercising in the heat. For the previously sedentary individual, an exercise regimen that incorporates 20 to 30 minutes of aerobic activity 3 to 4 days a week will improve cardiovascular function after 8 weeks.

It is important to remember that even physically active individuals may lack physical conditioning relative to a particularly stressful competition or activity. Heat illness in runners commonly occurs when novices exceed their training effort during

paces or when well-trained athletes increase their pace above normal during long-distance events.

Acclimatization

During initial exposure to a hot environment, workouts should be moderate in intensity and duration. A gradual increase in the time and intensity of physical exertion over 8 to 10 days should allow for optimal acclimatization.³³ Early season high-school heat-stroke deaths are most likely to occur during the first 4 days of practice⁸⁷; children require 10 to 14 days to achieve an appropriate acclimatization response. Acclimatization can be induced by simulating hot environmental conditions indoors. Aerobic activity should be conducted during exposure to the hot environment so that the individual can achieve optimal acclimatization.⁹⁰ If symptoms of heat illness develop during the acclimation period, all physical activity should be stopped and appropriate interventions begun. Acclimatization is not facilitated by restricting fluid intake; in fact, conscious attention to fluid intake is required to prevent dehydration. As with physical conditioning, there are limits to the degree of protection that acclimatization provides from heat stress. Given a sufficiently hot and humid environment, no one is immune to heat injury.

RESEARCH

Areas for future research include improved clarification of when athletes can safely return to play; the role of autonomic nervous system dysfunction in EHS; the benefit of induced hypothermia for EHS treatment; and the role of clonidine, activated protein C, and antibiotics during initial treatment.

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REFERENCES

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