REVIEW ARTICLE

Dan L. Longo, M.D., *Editor*

Heatstroke

Yoram Epstein, Ph.D., and Ran Yanovich, Ph.D.

Heatstroke is the most hazardous condition in a spectrum of illnesses progressing from heat exhaustion to heatstroke, in which a shared finding is hyperthermia (i.e., the rise in core body temperature when heat accumulation overrides heat dissipation during exercise or exposure to environmental heat stress).[1] Clinically, heatstroke is characterized by central nervous system (CNS) dysfunction, multiorgan failure, and extreme hyperthermia (usually >40.5°C).[2,3] This review summarizes current knowledge about heatstroke, which is often misinterpreted or overlooked, focusing on its relevance for medical practitioners.

From the Heller Institute of Medical Research, Sheba Medical Center (Y.E., R.Y.), and Sackler Faculty of Medicine, Tel Aviv University (Y.E.) — both in Tel Aviv, Israel; and Wingate College for Physical Education and Sport Sciences, Wingate Institute, Netanya, Israel (R.Y.). Address reprint requests to Dr. Epstein at the Heller Institute of Medical Research, Sheba Medical Center, Ramat Gan 52621, Israel, or at yoram.epstein@sheba.health.gov.il.

N Engl J Med 2019;380:2449-59.
DOI: 10.1056/NEJMra1810762

Classification, Risk Factors, and Epidemiology

Depending on its cause, heatstroke may be categorized as either classic (passive) or exertional. Both types derive from failure to dissipate excessive body heat, but their underlying mechanisms differ. Classic heatstroke is due to exposure to environmental heat and poor heat-dissipation mechanisms, whereas exertional heatstroke is associated with physical exercise and results when excessive production of metabolic heat overwhelms physiological heat-loss mechanisms (Table 1).

Classic Heatstroke

Classic heatstroke frequently occurs as an epidemic among elderly persons whose ability to adjust physiologically to heat stress has become compromised, chronically ill persons, and those who cannot care for themselves.[4,5] Rising global temperatures causing heat waves, as well as urbanization with its attendant inner-city heat islands, are the major extrinsic factors.[5,6] According to the U.S. National Weather Service, heat waves kill more people, on average, than any other extreme weather event.[6] Multiple intrinsic physiological, social, and medical risk factors render elderly persons more vulnerable to ongoing heat owing to their diminished thermoregulatory capacity (Table 2).[4,5,7-9] Consequently, many elderly patients with classic heatstroke are hospitalized or are found dead within 1 to 3 days after a reported onset of illness,[10,11] and mortality from heatstroke among the elderly exceeds 50%.[1,5]

Prepubertal children are also regarded as a population at risk.[12] Children's susceptibility to classic heatstroke is attributed to a high ratio of surface area to mass (leading to an increased heat-absorption rate), an underdeveloped thermoregulatory system (impairing effective heat dissipation), small blood volume relative to body size (limiting the potential for heat conductance and resulting in greater heat accumulation), and a low sweating rate (reducing the potential for heat dissipation through sweat evaporation).[13] In infants, a major risk factor for death during hot weather is confinement in a closed car, where death can occur within a few hours.[14]

Table 1. Epidemiologic and Clinical Features of Classic and Exertional Heatstroke.

Feature*	Classic Heatstroke	Exertional Heatstroke
Age group	Prepubertal, elderly	Postpubertal and active
Occurrence	Epidemic (heat waves)	Sporadic (any time of year)
Concurrent activity	Sedentary	Strenuous
Health status	Chronically ill	Generally healthy
Medications	Often being used (prescribed medications)	Usually none being used (sometimes ergogenic aids, illicit drugs)
Mechanism	Absorption of environmental heat and poor heat dissipation	Excessive heat production, which overwhelms heat-loss mechanisms
Sweating	May be absent (dry skin)	Usually present (wet skin)
CNS dysfunction	Common	Common
Acid–base disturbance	Respiratory alkalosis	Metabolic acidosis
Rhabdomyolysis	Unusual	Frequent
Liver dysfunction	Mild	Marked to severe
Renal failure	Uncommon (<5%)	Common (25–30%)
DIC	Mild	Marked to severe
ARDS	Common	Common
Creatine kinase	Mildly elevated	Markedly elevated
Calcium	Normal	Low (hypocalcemia)
Potassium	Normal	Usually high (hyperkalemia)

* ARDS denotes acute respiratory distress syndrome, CNS central nervous system, and DIC disseminated intravascular coagulation.

EXERTIONAL HEATSTROKE

Exertional heatstroke is a medical emergency, sporadic in nature, and directly related to strenuous physical activity. It can strike athletes, laborers (e.g., firefighters and agricultural workers), soldiers, and others engaging in activities that many of them previously performed uneventfully under similar conditions of exercise intensity and duration and environmental exposure. Exertional heatstroke can occur even within the first 60 minutes of exertion and may be triggered without exposure to high ambient temperatures.[15,16]

Overmotivation and pressure from peers and coaches that drive people to perform beyond their physiological capability are major risk factors for exertional heatstroke.[17] In addition, functional and acquired factors and some congenital conditions increase susceptibility to heat, leading to exertional heatstroke (Table 2).[18,19] Alcohol and drug abuse, alone or in combination, which are often a feature of psychedelic-trance music parties or festivals, heighten the metabolic response to energetic music[20] and are risk factors for exertional heatstroke among participants in these events. In addition, amphetamine-like drugs and other stimulating agents[21] are a major risk factor for exertional heatstroke in athletes (Table 2). Although previous heatstroke has been suggested as a risk factor for a recurrent episode,[22] this is not supported by conclusive evidence.

The true incidence of exertional heatstroke is unknown because of frequent misdiagnosis (e.g., as dehydration or heat exhaustion). Epidemiologic surveys of U.S. high-school football players[23] and army personnel[24] reveal a steady increase in morbidity and mortality from exertional heatstroke during the past decade. Nevertheless, because exertional heatstroke most often affects healthy young persons and its recognition and treatment are usually prompt, mortality rates are low (<5%).[1,3]

PATHOGENESIS AND PATHOPHYSIOLOGY

The primary pathogenic mechanism of heat stroke involves transition from a compensable thermoregulatory phase (in which heat loss exceeds heat gain) to a noncompensable phase (in which heat gain is greater than heat loss), when cardiac output is insufficient to cope with the high thermoregulatory needs. Consequently, core body temperature continues to rise, leading to a direct cytotoxic effect and an inflammatory response, creating a vicious cycle, and eventually causing multiorgan failure (Fig. 1).[1,2,25-27]

INFLAMMATORY RESPONSE

The cascade of events underlying the systemic inflammatory reaction in heatstroke awaits full elucidation. Hyperthermia triggers a coordinated stress response involving endothelial cells, leukocytes, and epithelial cells, which provide protection against tissue injury and promote cell repair. This reaction is mediated by the molecular chaperone family of heat-shock proteins and by changes in plasma and tissue levels of proinflammatory and antiinflammatory cytokines.[28-30] With prolonged hyperthermia, the acute physiological alterations (including circulatory failure, hypoxemia, and increased metabolic demands) and direct

Table 2. Risk Factors Underlying Heatstroke.*

Heatstroke Type and Risk Factor	Explanation
Classic	
Weather	Heat waves, with successive hot days and nights
Physiological factors	Cardiovascular insufficiency impeding normal cardiovascular adjustments to heat stress: inability to maintain acceptable stroke volume in the heat, inadequate peripheral vasodilatation due to structural changes and compromised nitric oxide–mediated vasodilatory mechanism, reduced capillary density and quality of cutaneous microcirculation, decreased sweat rate and sweat-gland output in response to heat stress
Social factors	Social isolation, unventilated and non–air-conditioned living space, inability to care for oneself, confinement to bed
Underlying illness	Exacerbation of mental, cardiovascular, cerebrovascular, and pulmonary illnesses and multiple sclerosis by exposure to heat stress
Medications	Beta-blockers, diuretics, calcium-channel blockers, laxatives, anticholinergic drugs, salicylates, thyroid agonists, benztropine, trifluoperazine, butyrophenones, α-agonists, monoamine oxidase inhibitors, sympathomimetic medications, tricyclic antidepressants, SSRIs
Exertional	
Social factors	Overmotivation, peer and coach pressure
Functional factors	Low physical fitness (physical effort unsuited to physical fitness; "killer workouts"), lack of acclimatization (habituation) to heat, low work efficiency, overweight (reduced ratio of skin area to mass and greater heat-storage capacity in fat layers), protective clothing (reduced sweating efficiency)
Acquired factors	Viral or bacterial infection (even if subclinical), dehydration, sleep deprivation, sweat-gland dysfunction (e.g., deep burns, scarred skin on >40% of total body-surface area)
Congenital factors	Chronic idiopathic or familial anhydrosis, ectodermal dysplasia
Drug abuse	Amphetamines and amphetamine-like agents (e.g., ephedra), MDMA, cocaine, PCP and LSD, synthetic stimulants of the cathinone class (e.g., α-PHP), alcohol

* LSD denotes lysergic acid diethylamide, MDMA 3,4-methylenedioxymethamphetamine (ecstasy), PCP phencyclidine, α-PHP α-pyrrolidinohexanophenone, and SSRI selective serotonin-reuptake inhibitor.

heat-related cytotoxic effects escalate, causing dysregulation of the inflammatory reaction.[31,32]

The heatstroke-related inflammatory response is akin to the systemic inflammatory response syndrome (SIRS).[2,33] It has been suggested that SIRS is mediated by circulating messenger RNAs that trigger the release of cytokines and the high-mobility group box 1 protein (HMGB1), leading to excessive activation of leukocytes and endothelial cells.[34,35] Much like septic shock, SIRS can cause a rapid deterioration in clinical status, resulting in disseminated intravascular coagulation (DIC), multiorgan failure, and death. Hence, heatstroke is considered to be "a form of hyperthermia associated with a systemic inflammatory response leading to a syndrome of multiorgan dysfunction in which encephalopathy predominates."[2] In a study of patients hospitalized for exertional heatstroke, 84% of the patients also met the diagnostic criteria for SIRS, and for those patients, hospitalization was prolonged.[36] Similarly, clinical and experimental evidence of neutrophil activation in classic heatstroke serves as a link between the inflammatory and coagulation responses.[32,33] Nevertheless, the association between SIRS and heatstroke may easily be overlooked because heatstroke, and especially exertional heatstroke, is not commonly seen in intensive care units and is not on the usual list of SIRS causes. The consequent delay in recognizing the etiologic link between the two disorders and administering appropriate treatment may dramatically exacerbate the clinical consequences of SIRS.

Gastrointestinal Integrity and Endotoxemia

The heatstroke-induced reduction in intestinal blood flow causes gastrointestinal ischemia, adversely affecting cell viability and cell-wall permeability. The resulting oxidative and nitrosative stress damages cell membranes and opens tight cell-to-cell junctions, allowing endotoxins and possibly pathogens to leak into the systemic circulation, overwhelming the detoxifying capacity of the liver and resulting in endotoxemia.[37,38]

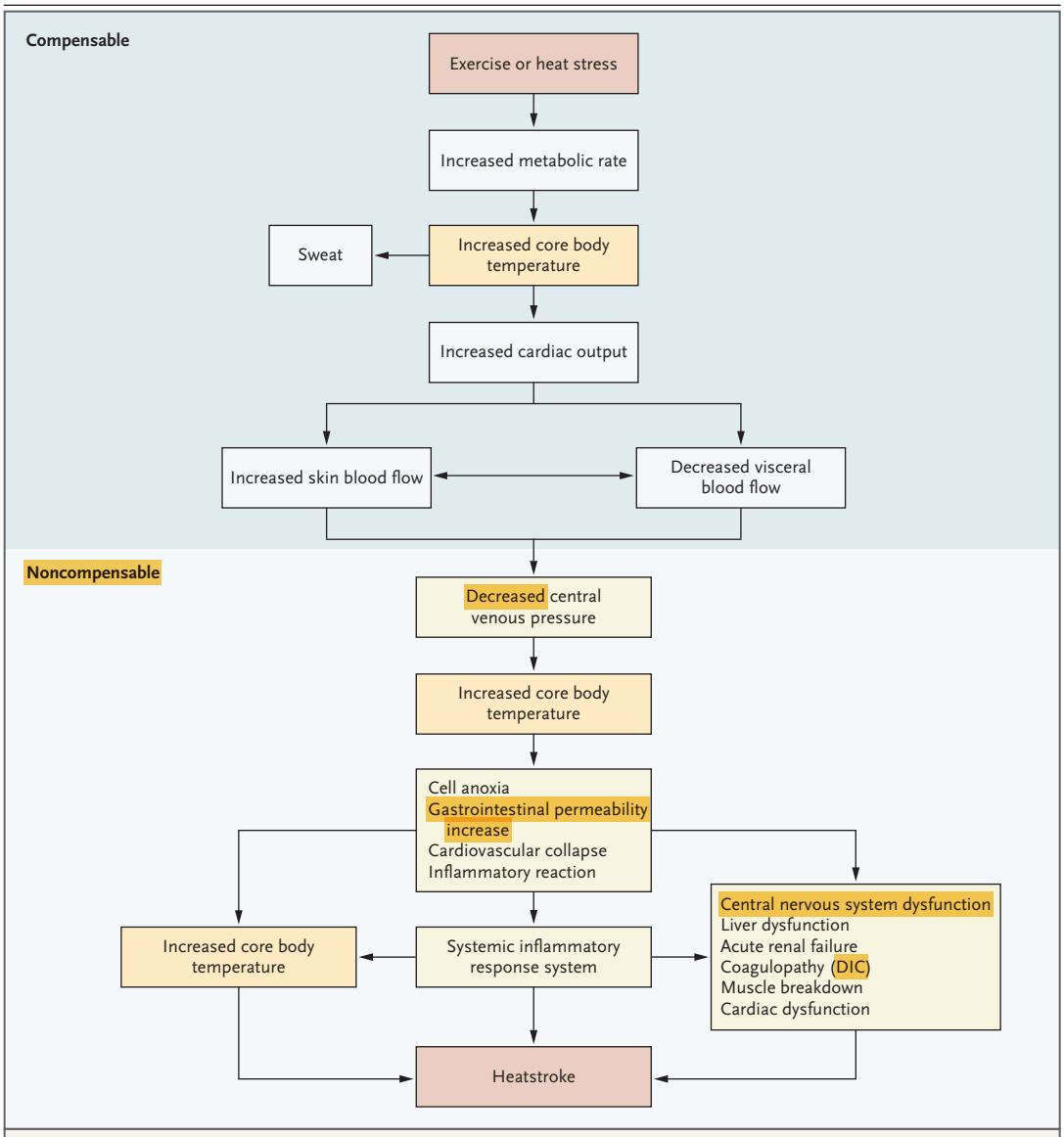

Figure 1. Pathophysiological Pathway Leading to Heat Stroke.

The sequence of events that leads to heat stroke involves a transition from a compensable thermoregulatory state to the noncompensable condition. Heat stress initiates a thermoregulatory response to increased cardiac output and redistribution of blood flow. When central venous pressure begins to decrease substantially, core temperature begins to increase rapidly and becomes noncompensable. The thermoregulatory failure aggravates pathophysiological processes at the cellular level, including an inflammatory reaction, and multiorgan failure occurs as a result of the combination of high body temperature and circulatory collapse, and ultimately is expressed as heatstroke. DIC denotes disseminated intravascular coagulation.

Although the concept of a link between heatstroke and endotoxemia is not new,[39] many physicians tend to ignore or misinterpret applicable laboratory findings. This can further exacerbate the clinical condition of patients with heatstroke and worsen the prognosis.

DIAGNOSIS

The diagnosis of heatstroke is largely clinical, based primarily on the triad of hyperthermia, neurologic abnormalities, and recent exposure to hot weather (in the classic form) or physical

exertion (in the exertional form). Tachycardia, tachypnea, and hypotension are common. Profuse sweating and wet skin are typical of exertional heatstroke, whereas in classic heatstroke, the skin is usually dry, reflecting the characteristic decrease in the sweat-gland response and output in elderly people under heat stress. The skin may be either flushed, reflecting excessive peripheral vasodilatation, or pale, indicating vascular collapse.

DIFFERENTIAL DIAGNOSIS

Any systemic disease with a similar clinical picture of fever and manifestations of brain dysfunction should be considered only after heatstroke has been ruled out, because a delay in the treatment of heatstroke substantially increases morbidity and mortality. Once heatstroke has been ruled out on the basis of the clinical history and context, other conditions to be considered include meningitis, encephalitis, epilepsy, drug intoxication (e.g., atropine, MDMA [3,4-methylenedioxymethamphetamine], cocaine, or amphetamines), severe dehydration, and any metabolic syndrome (e.g., neuroleptic malignant syndrome, lethal catatonia, serotonin syndrome, thyroid storm, or pheochromocytoma multisystem crisis).[1,40]

CLINICAL PICTURE AND COMPLICATIONS

The clinical picture of heatstroke has been extensively reviewed.[3,41] The disorder has three phases, which are seen more clearly in exertional heatstroke than in classic heatstroke: a hyperthermic–neurologic acute phase, a hematologic–enzymatic phase (peaking 24 to 48 hours after the event), and a late renal–hepatic phase (if clinical symptoms are sustained for 96 hours or longer). Most critical for primary care practitioners is the acute phase, since prompt recognition and treatment of heatstroke in the acute phase may be lifesaving.

Adequate measurement of core (rectal) temperature is critical in persons who may have heatstroke. Hyperthermia is expected, but reliance on a core body temperature of more than 40.5°C as a diagnostic yardstick could be misleading, since the temperature may be falsely low if the measurement is delayed or performed inappropriately (e.g., if temperature is measured orally or from the forehead or the axilla).[3,42] Nevertheless, extreme hyperthermia during physical exertion does not always indicate heatstroke; many marathon runners finish the race with a high core body temperature but without accompanying changes associated with the clinical picture of heatstroke.[43]

Given the brain's extreme sensitivity to hyperthermia, CNS disturbances are inevitable in heatstroke. Early symptoms include behavioral changes, confusion, delirium, dizziness, weakness, agitation, combativeness, slurred speech, nausea, and vomiting.[1] Seizures and sphincter incontinence may occur in severe cases, mainly in exertional heatstroke.[3]

Consciousness commonly deteriorates but is usually regained once the temperature falls below the critical level of 40.5°C. In severe cases, brain edema ensues.[1,3] Brain injury appears to be concentrated in the cerebellum, with generalized atrophy and evidence of involvement of the Purkinje cell layer.[41,44] Neuronal injury to the autonomic and enteric nervous systems may be long-lasting. The hypothesis that damage to the preoptic anterior hypothalamus is responsible for the loss of thermoregulation has not been proved.[1]

Multiorgan system dysfunction and failure (more pronounced in exertional heatstroke than in classic heatstroke) may peak within 24 to 48 hours (Table 1). If treatment is prompt, clinical signs become milder in most cases and abate within a few days, and most patients recover without lasting effects. Possible complications range from sustained alteration in consciousness to DIC, acute respiratory distress syndrome, and acute renal, cardiac, and hepatic dysfunction and failure.[2,3] Rhabdomyolysis, although not pathognomonic, is typical of exertional heatstroke.[3] The prognosis worsens when kidney and liver dysfunction are sustained for more than 96 hours. Autopsy studies show that end-organ failure after heatstroke is due primarily to heat-induced necrotic and apoptotic cell death accompanying widespread microthrombosis, hemorrhage, and inflammatory injury.[26,32,41] Some neurologic sequelae (e.g., cerebellar ataxia, dysarthria, cognitive disorders, and anterograde amnesia) may persist for several weeks to months.[45] One study indicates that the risk of death during the months and years after recovery from heatstroke may be higher than the risk in the general population.[46]

BIOMARKERS

Clinical and laboratory measures reflecting organ function should be systematically monitored

for at least 72 hours to avoid missing possible clinical deterioration.[3] However, experimental data indicate that these measures may not adequately reflect the severity of illness or the long-term prognosis.[1] Circulating biochemical markers that might better indicate organ failure and facilitate an accurate diagnosis and prompt treatment are under investigation, including HMGB1,[47] neutrophil gelatinase–associated lipocalin (also known as 24p3, uterocalin, and neu-related lipocalin),[48] cardiac troponin I,[49] the ratio of urinary heat shock protein 72 to urinary creatinine,[50] histone,[51] and cryptdin 2 peptide (an intestinal alpha-defensin).[52] However, these biomarkers are experimental and have not been clinically tested or approved.

TREATMENT

Patients with heatstroke are treated symptomatically and conservatively (Table 3). The primary objective is alleviation of hyperthermia; thus, unlike in other traumatic conditions, "cool and run" rather than "scoop and run" is the catchphrase.

CONTROL OF BODY TEMPERATURE

The prognosis worsens if the core body temperature is sustained above the critical threshold of 40.5°C. Indeed, rapid and effective cooling is the cornerstone of treatment and should be delayed only for essential cardiopulmonary resuscitation.[3,53] In the absence of a specifically defined end-point temperature for safe cessation of cooling, common practice dictates a target temperature below 39°C (preferably 38.5° to 38.0°C) to lessen the risk of clinical deterioration.[3]

For exertional heatstroke, a cooling rate faster than 0.10°C per minute is safe and is desirable for improving the prognosis.[54] Immersion in cold water for the treatment of exertional heatstroke is the accepted method of choice for achieving a cooling rate of 0.20° to 0.35°C per minute,[53,54] despite numerous reasons, all unfounded, for not using this method.[53] Under military or desert field conditions where ice is not readily available, a cooling rate of approximately 0.10°C per minute can be achieved by pouring copious amounts of water over the body and fanning.[54,55]

In elderly persons with classic heatstroke, cold-water immersion can yield an acceptable cooling rate, but the treatment of choice involves the use of one or more types of conductive or evaporative cooling, such as infusion of cold fluids (intravascular temperature management); application of ice packs, cold packs, or wet gauze sheets; and fanning. These methods, albeit less efficient than cold-water immersion, are better tolerated by elderly persons and are also readily accessible and easily applied during an epidemic of classic heatstroke, when emergency depart-

Table 3. Guidelines for the Treatment of Heatstroke.*

Treatment	Comments
Treatment on site	
CPR	Perform according to ACLS protocol; administer oxygen at 4 liters/min to increase oxygen saturation to >90%
Core body temperature	Monitor rectal temperature and perform cooling in cases of hyperthermia; for exertional heatstroke, cold-water immersion; for classic heatstroke, conductive or evaporative cooling
Fluids	Administer isotonic saline IV (1–2 liters/hr); dehydration is not a major issue
Seizure medication	Administer benzodiazepines IV (5 mg) until seizures cease (not more than 20 mg)
Evacuation	For classic heatstroke, transport immediately to ED; for exertional heatstroke, transport to ED after cooling to body temperature <39.0°C
Treatment in the ED	
Core body temperature	Monitor rectal or intravesical temperature and perform cooling until core temperature <38.0°C; use either a cooling suit or cold fluids (4°C, 1000 ml/30 min) infused through central catheter; antipyretics are toxic and should be avoided; dantrolene has not been proved to be effective
Seizure medication	Administer benzodiazepines IV (5 mg, repeated) or phenytoin IV (loading dose, 15–20 mg/kg in 15 min) until seizures cease
Laboratory testing	Perform CBC, urinalysis, blood cultures, kidney-function and liver-function tests (ALT, AST, ammonia, INR); test for glucose, electrolytes, arterial blood gases and acid–base balance, clotting function, CK, LDH, myoglobin, CRP

Table 3. (Continued.)

Treatment	Comments
Monitoring of circulation	For circulatory failure, administer fluids (30 ml/kg), monitor CVP or perform invasive hemodynamic monitoring, maintain mean arterial pressure at >65 mm Hg (or >75 mm Hg if patient is elderly or has hypertension), all with a goal of normal lactate level and urine output >50 ml/kg/hr; vasopressors should be considered if fluid therapy fails
Treatment in the ICU	
General	Perform CPR according to ACLS protocol; ECMO may be used as needed
	Monitor rectal, intravesical, or blood temperature; continue cooling to maintain core temperature at <38.0°C by infusing cold fluids (4°C, 1000 ml/30 min) through central catheter or use extracorporeal blood cooling for resistant hyperthermia; antipyretics are toxic and should be avoided; dantrolene has not been proved to be effective
	Perform laboratory tests: CBC, glucose, arterial blood gases and acid–base balance, clotting function, CK, LDH, liver function (ALT, AST, ammonia, INR), myoglobin, kidney function, urinalysis, CRP, blood cultures; repeat every 12 hr during the first 48 hr, then every 24 hr
Heart failure	Perform CPR according to ACLS protocol; perform invasive hemodynamic monitoring and echocardiography; for mild multiorgan failure, administer dobutamine IV (1 μg/kg/min, then 2–20 μg/kg/min as needed) or milrinone IV (loading dose, 50 μg/kg in 10 min, then 0.2–0.75 μg/kg/min) or adrenaline IV (1 μg/min); for severe multiorgan failure, ECMO may be used as needed
Acute kidney injury	Administer crystalloid solution to maintain urine output >50 ml/kg/hr; administer furosemide IV (10–20 mg in patients without previous exposure to diuretics; follow-up dose depends on urine output); provide hemodialysis or CVVH in cases of volume overload, severe acidosis, hyperkalemia, or uremia; adjust fluid infusion rate according to blood pressure and urine output; monitor electrolytes and correct as needed
Encephalopathy and brain edema	For a score of <8 on the GCS,† intubate and ventilate; for mild hyperventilation (P_{CO_2}, 34–36 mm Hg) administer hypertonic saline 3% IV (starting dose, 100 ml/30 min, then according to patient's total body water to reach sodium level increase of 12 mmol/day) or mannitol 20% IV (0.25–2 g/kg in 30 min); keep head at 45-degree angle, administer tranquilizers; patients with hyperammonemia require hemofiltration or MARS therapy; condition improves with cooling; consider monitoring ICP
Rhabdomyolysis	Administer IV fluid infusion, 1–2 liters/hr (aggressive fluid treatment in the first hour), then 300 ml/hr; furosemide IV (10–20 mg in patients without previous diuretic treatment; follow-up dose depends on urine output) in case of fluid overload; sodium bicarbonate, 30 mmol/hr (to achieve urine pH >6.5); myoglobinuria is expected; hypercalcemia and metabolic alkalosis (pH >7.5) should be avoided
DIC and other coagulation abnormalities	For bleeding and thrombosis, administer fresh-frozen plasma (bolus dose, 10–15 ml/kg, then 200–400 ml according to coagulation indexes); administer cryoprecipitate (5–10 U each time) for fibrinogen level of <180 mg/dl; administer platelet concentrates (infusion of one therapeutic dose) if platelet count <20 per mm^3 or if there is bleeding and platelet count <50 per mm^3; in patients with hepatic failure, consider PCC to achieve a target INR ≤1.5; inject PCC dose according to INR and patient's weight; avoid heparin; beware of hypothermia and metabolic acidosis
ARDS	Perform intubation and mechanical ventilation; avoid fluid overload
Liver failure	Monitor liver function and mental status for at least 4 days; provide supportive treatment: hemodynamic stability, *N*-acetylcysteine IV (bolus dose, 150 mg/kg in 200 ml of 5% glucose solution for 20 min, then 50 mg/kg in 500 ml of 5% glucose solution for 4 hr, then 100 mg/kg in 1000 ml of 5% glucose solution for 16 hr); administer hypertonic saline 3% IV or mannitol IV (0.25–2 g/kg in 30 min in 20% solution), hemofiltration, laxatives (e.g., oral lactulose, 30 ml every 2 hr until diarrhea occurs), oral rifaximin (400 mg 3 times a day) in case of fulminant liver failure; liver transplantation rarely needed, and there is no evidence that it is effective
ECG changes	Monitor continuously for possible arrhythmias; ECG changes are nonspecific
SIRS	Treat the same as sepsis; consider antibiotics

* The recommendations given in this table are general guidelines. Individualized treatment according to the patient's condition is advised. The full picture of organ failure may be evident only 24 to 48 hours after the event. Therefore, follow-up should continue for at least 96 hours. ACLS denotes advanced cardiovascular life support, ALT alanine aminotransferase, AST aspartate aminotransferase, CBC complete blood count, CK creatine kinase, CPR cardiopulmonary resuscitation, CRP C-reactive protein, CVP central venous pressure, CVVH continuous venovenous hemofiltration, ECG electrocardiography, ECMO extracorporeal membrane oxygenation, ED emergency department, ICP intracranial pressure, ICU intensive care unit, INR international normalized ratio, IV intravenous, LDH lactate dehydrogenase, MARS molecular adsorption recirculation system, PCC prothrombin complex concentrate, P_{CO_2} partial pressure of carbon dioxide, and SIRS systemic inflammatory response syndrome.

† Scores on the Glasgow Coma Scale (GCS) range from 3 to 15, with lower scores indicating a reduced level of consciousness.

ments may be inundated with frail elderly patients.[56]

No pharmacologic agents accelerate cooling. Antipyretic agents such as aspirin and acetaminophen are ineffective in patients with heatstroke, since fever and hyperthermia raise the core body temperature through different physiological pathways. Furthermore, antipyretic agents aggravate coagulopathy and liver injury in patients with heatstroke. The ryanodine receptor antagonist dantrolene, used in the treatment of malignant hyperthermia, is under investigation for heatstroke therapy (ClinicalTrials.gov number, NCT03600376), but there is currently no evidence to support the claim that this agent is effective for heatstroke. Indeed, the release of skeletal-muscle calcium appears to have no role in the pathophysiology of heatstroke.[1,40]

TREATMENT OF ORGAN INJURIES

Prompt recognition and effective cooling will in most cases rapidly reverse heat-induced organ dysfunction. However, cooling may not suffice to effect a full recovery, and prompt administration of adjuvant treatments may be critical for survival. The standard of care should be immediate intervention with symptomatic support of organ functions and awareness of the possible development of SIRS (Table 3).[3,35]

Several novel treatment approaches, which could presage future therapies, are being investigated in animal models and in preliminary clinical studies. These include a xanthine oxidase inhibitor (allopurinol) to reduce portal lipopolysaccharide levels by protecting the integrity of tight cell-to-cell junctions,[37] recombinant activated protein C to ameliorate inflammation and the dysfunctional coagulation cascade,[57] type III antithrombin concentrate and recombinant soluble thrombomodulin-α to treat DIC[58,59] (and NCT00487656), and serine proteases to suppress pancreatic enzyme activity in the intestinal lumen, thereby substantially reducing systemic inflammatory markers.[60] Adjuvant treatment with Chinese rhubarb, a plant species of the Polygonaceae family, reportedly alleviates the inflammatory response and facilitates recovery from heat-associated acute liver and kidney injury[61] (Chinese Clinical Trial Registry number, ChiCTR1800016460). These potential therapies are at different stages of investigation, and the data are still limited. More information and experience will be required before they can be approved for use in patients.

PREVENTION

Prevention of heatstroke is more effective than treatment and is certainly easier. In warm weather and especially during heat waves, protective steps should be taken to mitigate the risk of classic heatstroke. These include staying in air-conditioned homes or other air-conditioned premises (e.g., shopping malls or movie theaters), using fans, taking frequent cool showers, decreasing exertion, and increasing social contact to counteract isolation.[4,62] In addition, family members, neighbors, and social workers are advised to check on elderly persons frequently to ensure their well-being.

Adherence to experience-based preventive measures at both the individual and organizational levels can significantly reduce the incidence of exertional heatstroke.[17] These measures include acclimatizing to changed environmental conditions, matching the level of physical exertion to the degree of physical fitness, avoiding hot times of the day for training schedules, removing vapor-barrier equipment and clothing that interfere with sweat evaporation, maintaining a proper hydration regimen, and scheduling rest periods during activity; persons with early signs of illness should be prevented from engaging in physical activity.[15,17]

RETURN TO NORMAL ACTIVITY AFTER HEATSTROKE

Elderly persons recovering from classic heatstroke should be helped to adopt a healthier lifestyle that will enable them to cope with heat stress. For workers, athletes, or military personnel recovering from exertional heatstroke, there are no comprehensive guidelines for returning to work, play, or duty. Common sense dictates waiting for clinical and laboratory findings to return to normal and cautiously reintroducing exercise.[19,63] The American College of Sports Medicine recommends a structured test of heat tolerance before an athlete returns to play but does not specify a protocol.[63,64] Two such tests exist for military personnel,[65,66] and although their effectiveness is still being debated,[67] they

appear to be in use as an auxiliary tool for deciding when soldiers may return to duty.

HEATSTROKE AND GENOMIC OR GENETIC TRAITS

Studies in a rat model exposed to heat stress and observations in patients with exertional heatstroke have shown marked genomic changes that are consistent with the hypothesis that heatstroke can result from the cumulative effects of multiple adverse interacting stimuli, including a possible genomic predisposition to heat intolerance.[68,69] This hypothesis may be further supported by the observations that the lymphocyte transcriptome differs from one person to another and that in persons considered to have heat intolerance, the transcription factors of cytoprotective genes are malfunctioning, possibly explaining the susceptibility of such persons to heat stress.[70] During acclimation to heat (a protective process that reduces the risk of heatstroke), genomic changes show a biphasic response in the rat hypothalamus: enhanced transcription of neuronal excitability-linked genes during early acclimation and enhanced metabolic efficiency when acclimatory homeostasis is achieved.[71] Whether heat-tolerant persons and heat-intolerant persons have different patterns of response to heat acclimation is not known. The accumulated data are still fragmentary, and genomic changes in most of the cases become apparent only when challenged by heat stress. Hence, further research is needed to substantiate the mechanistic significance of genomic changes in patients with heatstroke.

Some clinical and experimental data support a probable association between exertional heatstroke and malignant hyperthermia.[72,73] In one clinical study, an unexpectedly high prevalence of the malignant hyperthermia susceptibility trait (45.6%) was detected among patients with exertional heatstroke.[74] Studies in a knockout mouse model identified *CASQ1* as a candidate gene for linkage analysis between the two conditions.[73] However, whether patients with exertional heatstroke are at above-average risk for malignant hyperthermia and whether susceptibility to that condition is a risk factor for exertional heatstroke are still unanswered questions.

The risk of exercise-related death among athletes and military personnel with the sickle-cell trait is higher than the risk among their counterparts who are not carriers of this trait.[75] However, no evidence supports an association between the sickle-cell trait and exertional heatstroke.[76]

CONCLUSIONS

Heatstroke is a life-threatening condition if it is not promptly recognized and effectively treated. Certain simple preventive measures, such as avoiding strenuous activity in hot environments and reducing exposure to heat stress, as well as changing attitudes in sports and addressing socioeconomic issues that augment risk, can reduce the prevalence of both classic and exertional heatstroke. Our understanding of the pathophysiology of heatstroke and mechanism-based treatment approaches is still incomplete. Future research is likely to focus on three areas: identifying genetic traits that might reduce a person's ability to cope with heat stress, searching for new biomarkers that can better predict short- and long-term outcomes of heatstroke, and developing new adjuvant treatments that can effectively control the inflammatory reaction and counteract multiorgan complications.

No potential conflict of interest relevant to this article was reported.

Disclosure forms provided by the authors are available with the full text of this article at NEJM.org.

We thank Dr. Yael Haviv at Sheba Medical Center for providing detailed management protocols for heatstroke complications.

REFERENCES

1. Leon LR, Bouchama A. Heat stroke. Compr Physiol 2015;5:611-47.
2. Bouchama A, Knochel JP. Heat stroke. N Engl J Med 2002;346:1978-88.
3. Shapiro Y, Seidman DS. Field and clinical observations of exertional heat stroke patients. Med Sci Sports Exerc 1990;22:6-14.
4. Bouchama A, Dehbi M, Mohamed G, Matthies F, Shoukri M, Menne B. Prognostic factors in heat wave related deaths: a meta-analysis. Arch Intern Med 2007;167:2170-6.
5. Kravchenko J, Abernethy AP, Fawzy M, Lyerly HK. Minimization of heatwave morbidity and mortality. Am J Prev Med 2013;44:274-82.
6. Office of Climate, Water, and Weather Services. Weather fatalities 2018. Silver Spring, MD: National Weather Service, April 2019 (http://www.nws.noaa.gov/om/hazstats.shtml).
7. Kenney WL, Craighead DH, Alexander LM. Heat waves, aging, and human cardiovascular health. Med Sci Sports Exerc 2014;46:1891-9.
8. Li L, Mac-Mary S, Sainthillier JM,

Nouveau S, de Lacharriere O, Humbert P. Age-related changes of the cutaneous microcirculation in vivo. Gerontology 2006; 52:142-53.
9. Anderson RK, Kenney WL. Effect of age on heat-activated sweat gland density and flow during exercise in dry heat. J Appl Physiol (1985) 1987;63:1089-94.
10. Fouillet A, Rey G, Laurent F, et al. Excess mortality related to the August 2003 heat wave in France. Int Arch Occup Environ Health 2006;80:16-24.
11. Åström DO, Forsberg B, Rocklöv J. Heat wave impact on morbidity and mortality in the elderly population: a review of recent studies. Maturitas 2011;69:99-105.
12. Heat-related deaths — United States, 1999–2003. MMWR Morb Mortal Wkly Rep 2006;55:796-8.
13. Falk B, Dotan R. Children's thermoregulation during exercise in the heat: a revisit. Appl Physiol Nutr Metab 2008; 33:420-7.
14. Booth JN III, Davis GG, Waterbor J, McGwin G Jr. Hyperthermia deaths among children in parked vehicles: an analysis of 231 fatalities in the United States, 1999-2007. Forensic Sci Med Pathol 2010; 6:99-105.
15. Epstein Y, Moran DS, Shapiro Y, Sohar E, Shemer J. Exertional heat stroke: a case series. Med Sci Sports Exerc 1999;31: 224-8.
16. Hosokawa Y, Adams WM, Belval LN, et al. Exertional heat illness incidence and on-site medical team preparedness in warm weather. Int J Biometeorol 2018;62: 1147-53.
17. Rav-Acha M, Hadad E, Epstein Y, Heled Y, Moran DS. Fatal exertional heat stroke: a case series. Am J Med Sci 2004;328:84-7.
18. Epstein Y. Heat intolerance: predisposing factor or residual injury? Med Sci Sports Exerc 1990;22:29-35.
19. O'Connor FG, Heled Y, Deuster PA. Exertional heat stroke, the return to play decision, and the role of heat tolerance testing: a clinician's dilemma. Curr Sports Med Rep 2018;17:244-8.
20. Nadesan K, Kumari C, Afiq M. Dancing to death: a case of heat stroke. J Forensic Leg Med 2017;50:1-5.
21. Reardon CL, Creado S. Drug abuse in athletes. Subst Abuse Rehabil 2014;5:95-105.
22. Abriat A, Brosset C, Brégigeon M, Sagui E. Report of 182 cases of exertional heatstroke in the French Armed Forces. Mil Med 2014;179:309-14.
23. Kerr ZY, Marshall SW, Comstock RD, Casa DJ. Implementing exertional heat illness prevention strategies in US high school football. Med Sci Sports Exerc 2014;46:124-30.
24. Armed Forces Health Surveillance Branch. Update: heat illness, active component, U.S. Armed Forces, 2017. MSMR 2018;25:6-12.
25. Epstein Y, Roberts WO. The pathophysiology of heat stroke: an integrative view of the final common pathway. Scand J Med Sci Sports 2011;21:742-8.
26. Roberts GT, Ghebeh H, Chishti MA, et al. Microvascular injury, thrombosis, inflammation, and apoptosis in the pathogenesis of heatstroke: a study in baboon model. Arterioscler Thromb Vasc Biol 2008; 28:1130-6.
27. Lim CL. Heat sepsis precedes heat toxicity in the pathophysiology of heat stroke — a new paradigm on an ancient disease. Antioxidants (Basel) 2018;7(11): E149.
28. Yang YL, Lin MT. Heat shock protein expression protects against cerebral ischemia and monoamine overload in rat heatstroke. Am J Physiol 1999;276:H1961-H1967.
29. Yan YE, Zhao YQ, Wang H, Fan M. Pathophysiological factors underlying heatstroke. Med Hypotheses 2006;67:609-17.
30. Dehbi M, Baturcam E, Eldali A, et al. Hsp-72, a candidate prognostic indicator of heatstroke. Cell Stress Chaperones 2010; 15:593-603.
31. Leon LR, Helwig BG. Heat stroke: role of the systemic inflammatory response. J Appl Physiol (1985) 2010;109:1980-8.
32. Bouchama A, Roberts G, Al Mohanna F, et al. Inflammatory, hemostatic, and clinical changes in a baboon experimental model for heatstroke. J Appl Physiol (1985) 2005;98:697-705.
33. Huisse MG, Pease S, Hurtado-Nedelec M, et al. Leukocyte activation: the link between inflammation and coagulation during heatstroke — a study of patients during the 2003 heat wave in Paris. Crit Care Med 2008;36:2288-95.
34. Caserta S, Mengozzi M, Kern F, Newbury SF, Ghezzi P, Llewelyn MJ. Severity of systemic inflammatory response syndrome affects the blood levels of circulating inflammatory-relevant microRNAs. Front Immunol 2018;8:1977.
35. Hifumi T, Kondo Y, Shimizu K, Miyake Y. Heat stroke. J Intensive Care 2018;6:30.
36. Zeller L, Novack V, Barski L, Jotkowitz A, Almog Y. Exertional heatstroke: clinical characteristics, diagnostic and therapeutic considerations. Eur J Intern Med 2011;22:296-9.
37. Hall DM, Buettner GR, Oberley LW, Xu L, Matthes RD, Gisolfi CV. Mechanisms of circulatory and intestinal barrier dysfunction during whole body hyperthermia. Am J Physiol Heart Circ Physiol 2001;280:H509-H521.
38. Snipe RMJ, Khoo A, Kitic CM, Gibson PR, Costa RJS. The impact of exertional-heat stress on gastrointestinal integrity, gastrointestinal symptoms, systemic endotoxin and cytokine profile. Eur J Appl Physiol 2018;118:389-400.
39. Brock-Utne JG, Gaffin SL, Wells MT, et al. Endotoxaemia in exhausted runners after a long-distance race. S Afr Med J 1988;73:533-6.
40. Epstein Y, Hadad E, Shapiro Y. Pathological factors underlying hyperthermia. J Therm Biol 2004;29:487-94.
41. Malamud N, Haymaker W, Custer RP. Heat stroke; a clinico-pathologic study of 125 fatal cases. Mil Surg 1946;99:397-449.
42. Mazerolle SM, Ganio MS, Casa DJ, Vingren J, Klau J. Is oral temperature an accurate measurement of deep body temperature? A systematic review. J Athl Train 2011;46:566-73.
43. Maron MB, Wagner JA, Horvath SM. Thermoregulatory responses during competitive marathon running. J Appl Physiol Respir Environ Exerc Physiol 1977;42:909-14.
44. Albukrek D, Bakon M, Moran DS, Faibel M, Epstein Y. Heat-stroke-induced cerebellar atrophy: clinical course, CT and MRI findings. Neuroradiology 1997; 39:195-7.
45. Yang M, Li Z, Zhao Y, et al. Outcome and risk factors associated with extent of central nervous system injury due to exertional heat stroke. Medicine (Baltimore) 2017;96(44):e8417.
46. Wallace RF, Kriebel D, Punnett L, Wegman DH, Amoroso PJ. Prior heat illness hospitalization and risk of early death. Environ Res 2007;104:290-5.
47. Tong HS, Tang YQ, Chen Y, Qiu JM, Wen Q, Su L. Early elevated HMGB1 level predicting the outcome in exertional heatstroke. J Trauma 2011;71:808-14.
48. Segev G, Daminet S, Meyer E, et al. Characterization of kidney damage using several renal biomarkers in dogs with naturally occurring heatstroke. Vet J 2015; 206:231-5.
49. Mellor PJ, Mellanby RJ, Baines EA, Villiers EJ, Archer J, Herrtage ME. High serum troponin I concentration as a marker of severe myocardial damage in a case of suspected exertional heatstroke in a dog. J Vet Cardiol 2006;8:55-62.
50. Bruchim Y, Avital Y, Horowitz M, Mazaki-Tovi M, Aroch I, Segev G. Urinary heat shock protein 72 as a biomarker of acute kidney injury in dogs. Vet J 2017; 225:32-4.
51. Bruchim Y, Ginsburg I, Segev G, et al. Serum histones as biomarkers of the severity of heatstroke in dogs. Cell Stress Chaperones 2017;22:903-10.
52. Ji J, Gu Z, Li H, Su L, Liu Z. Cryptdin-2 predicts intestinal injury during heat-

stroke in mice. Int J Mol Med 2018;41:137-46.
53. Casa DJ, McDermott BP, Lee EC, Yeargin SW, Armstrong LE, Maresh CM. Cold water immersion: the gold standard for exertional heatstroke treatment. Exerc Sport Sci Rev 2007;35:141-9.
54. McDermott BP, Casa DJ, Ganio MS, et al. Acute whole-body cooling for exercise-induced hyperthermia: a systematic review. J Athl Train 2009;44:84-93.
55. Heled Y, Rav-Acha M, Shani Y, Epstein Y, Moran DS. The "golden hour" for heatstroke treatment. Mil Med 2004;169:184-6.
56. Bouchama A, Dehbi M, Chaves-Carballo E. Cooling and hemodynamic management in heatstroke: practical recommendations. Crit Care 2007;11(3):R54.
57. Chen CM, Hou CC, Cheng KC, Tian RL, Chang CP, Lin MT. Activated protein C therapy in a rat heat stroke model. Crit Care Med 2006;34:1960-6.
58. Pechlaner C, Kaneider NC, Djanani A, Sandhofer A, Schratzberger P, Patsch JR. Antithrombin and near-fatal exertional heat stroke. Acta Med Austriaca 2002;29:107-11.
59. Vincent JL, Ramesh MK, Ernest D, et al. A randomized, double-blind, placebo-controlled, phase 2b study to evaluate the safety and efficacy of recombinant human soluble thrombomodulin, ART-123, in patients with sepsis and suspected disseminated intravascular coagulation. Crit Care Med 2013;41:2069-79.
60. DeLano FA, Hoyt DB, Schmid-Schönbein GW. Pancreatic digestive enzyme blockade in the intestine increases survival after experimental shock. Sci Transl Med 2013;5:169ra11.
61. Wan Y, Sun SS, Fu HY, et al. Adjuvant rhubarb alleviates organs dysfunction and inhibits inflammation in heat stroke. Exp Ther Med 2018;16:1493-8.
62. Hajat S, O'Connor M, Kosatsky T. Health effects of hot weather: from awareness of risk factors to effective health protection. Lancet 2010;375:856-63.
63. O'Connor FG, Casa DJ, Bergeron MF, et al. American College of Sports Medicine Roundtable on exertional heat stroke — return to duty/return to play: conference proceedings. Curr Sports Med Rep 2010;9:314-21.
64. Armstrong LE, Casa DJ, Millard-Stafford M, Moran DS, Pyne SW, Roberts WO. American College of Sports Medicine position stand: exertional heat illness during training and competition. Med Sci Sports Exerc 2007;39:556-72.
65. Schermann H, Craig E, Yanovich E, Ketko I, Kalmanovich G, Yanovich R. Probability of heat intolerance: standardized interpretation of heat-tolerance testing results versus specialist judgment. J Athl Train 2018;53:423-30.
66. Roiz de Sa D, House C. Exercise heat tolerance assessment following a diagnosis of heat illness in UK military personnel. Extrem Physiol Med 2015;4:Suppl 1:A105.
67. Roberts WO, Dorman JC, Bergeron MF. Recurrent heat stroke in a runner: race simulation testing for return to activity. Med Sci Sports Exerc 2016;48:785-9.
68. Sonna LA, Wenger CB, Flinn S, Sheldon HK, Sawka MN, Lilly CM. Exertional heat injury and gene expression changes: a DNA microarray analysis study. J Appl Physiol (1985) 2004;96:1943-53.
69. Zhang HJ, Drake VJ, Morrison JP, Oberley LW, Kregel KC. Selected contribution: differential expression of stress-related genes with aging and hyperthermia. J Appl Physiol (1985) 2002;92:1762-9.
70. Horowitz M, Kopeliovitch D, Berdugo R, et al. Revisiting heat tolerance: gene expression profiling response. In: Proceedings of the 7th International Conference on the Physiology and Pharmacology of Temperature Regulation, Split, Croatia, October 7–12, 2018:58.
71. Schwimmer H, Eli-Berchoer L, Horowitz M. Acclimatory-phase specificity of gene expression during the course of heat acclimation and superimposed hypohydration in the rat hypothalamus. J Appl Physiol (1985) 2006;100:1992-2003.
72. Poussel M, Guerci P, Kaminsky P, et al. Exertional heat stroke and susceptibility to malignant hyperthermia in an athlete: evidence for a link? J Athl Train 2015;50:1212-4.
73. Protasi F, Paolini C, Dainese M. Calsequestrin-1: a new candidate gene for malignant hyperthermia and exertional/environmental heat stroke. J Physiol 2009;587:3095-100.
74. Sagui E, Montigon C, Abriat A, et al. Is there a link between exertional heat stroke and susceptibility to malignant hyperthermia? PLoS One 2015;10(8):e0135496.
75. Harmon KG, Drezner JA, Klossner D, Asif IM. Sickle cell trait associated with a RR of death of 37 times in National Collegiate Athletic Association football athletes: a database with 2 million athlete-years as the denominator. Br J Sports Med 2012;46:325-30.
76. Nelson DA, Deuster PA, O'Connor FG, Kurina LM. Sickle cell trait and heat injury among US Army soldiers. Am J Epidemiol 2018;187:523-8.

IMAGES IN CLINICAL MEDICINE

The *Journal* welcomes consideration of new submissions for Images in Clinical Medicine. Instructions for authors and procedures for submissions can be found on the *Journal*'s website at NEJM.org. At the discretion of the editor, images that are accepted for publication may appear in the print version of the *Journal*, the electronic version, or both.