Chapter 24

EXERTIONAL HEAT ILLNESSES

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INTRODUCTION

Exertional heat illness (EHI)—which occurs as a result of exercising in high temperatures, exercising while dehydrated or with an electrolyte imbalance, or a combination of both—is a common medical emergency encountered in the US military service, particularly significant during initial entry training. This condition ranges across a continuum of increasing severity, from heat exhaustion to heat injury and heatstroke. EHI results from a progression of heat strain that causes cardiovascular responses, thus reducing perfusion and hyperthermia and inducing heat shock to body tissues (eg, brain, endothelium, hepatic, renal, and muscle). The net effect is necrosis, apoptosis, coagulopathy, and inflammation that results in damage to the organs and the

TABLE 24-1

REPORTED HEAT-RELATED INJURY RATES AMONG NEWLY ACCESSIONED OFFICERS, 1998–2003*

	1998	1999	2000	2001	2002	2003
DoD						
Heatstroke	0.73	2.72	0.35	1.82	1.9	0.4
Heat exhaustion	6.57	5.78	12.84	8.2	7.23	3.56
Other	2.92	1.02	1.39	4.1	4.19	2.77
US Army						
Heatstroke	2.13	4.82	0	1.4	5.58	1.45
Heat exhaustion	13.87	8.67	7.47	18.17	11.15	8.68
Other	8.53	1.93	1.87	6.99	9.76	8.68
US Navy						
Heatstroke	0	0	0	1.63	0	0
Heat exhaustion	1.38	0	1.31	0	3.2	0
Other	0	1.44	0	1.63	1.6	0
US Marine Corps						
Heatstroke	0	10.83	3.7	8.21	4.14	0
Heat exhaustion	12.53	28.87	66.64	12.31	28.96	3.99
Other	0	0	3.7	4.1	8.27	0
US Air Force						
Heatstroke	0	0	0	0	0	0
Heat exhaustion	1.19	0	12.86	3.22	1.92	2.1
Other	0	0	1.29	3.22	0.96	1.05

*Includes the *International Classification of Diseases, Ninth Revision, Clinical Modification* (*ICD-9-CM*) codes 992.0–992.9, based on DoD Reportable Medical Events (RMES, NDRS, and AFRESS) and Defense Medical Surveillance System hospitalization and outpatient databases. A newly accessioned officer has < 1 year of service at the time of diagnosis and a rank of O3 or less. Reportable medical events data available since 1994, NDRS data available since 2001, and AFRESS data available since 2001. Outpatient data available since 1996. Rates are per 1,000 person-years.

DoD: Department of Defense

RMES: Reportable Medical Events System

NDRS: Naval Disease Reporting System

AFRESS: Air Force Reportable Events Surveillance System

O3: military rank in the Army = Captain, Navy = Lieutenant, Marines = Captain, Air Force = Captain

Data source: Defense Medical Surveillance System, US Army Medical Surveillance Activity, US Army Center for Health Promotion and Preventive Medicine, June 16, 2004.

central nervous system (CNS) via fever, shock, disseminated intravascular coagulation, hemorrhage, stroke, and rhabdomyolysis.

Summary data among military populations have identified summer season, younger age, female gender, Caucasian race, enlisted rank, increased body mass index, poor physical conditioning, and recent enrollment (< 1 year) in the military as risk factors for the development of EHI.[1-4] In addition, lack of heat acclimation and dehydration accentuate these risks. Because a large percentage of young recruits possess these characteristics, prevention of EHI is critical to maintaining soldier health and training effectiveness.

Recruits often engage in intense outdoor training in hot environments before they are physically conditioned or heat acclimated. Most US military basic training installations are located in hot climates (eg, Georgia, South Carolina, Texas, and California):

US Army
- Fort Benning, Georgia
- Fort Jackson, South Carolina

TABLE 24-2

REPORTED HEAT-RELATED INJURY RATES AMONG RECRUITS, 1998–2003*

	DoD					
	1998	**1999**	**2000**	**2001**	**2002**	**2003**
Heatstroke	3.76	3.47	2.44	3.47	4.31	4.67
Heat exhaustion	17.35	19.82	23.16	25.4	33.61	25.53
Other	14.24	17.09	24.12	25.17	28.4	21.18
	US Army					
Heatstroke	3.76	4.29	2.26	3.78	3.63	3.06
Heat exhaustion	20.92	23.79	25.05	29.03	33.93	21.44
Other	11.2	13.25	20.77	25.01	33.36	21.77
	US Navy					
Heatstroke	0.42	0.41	0.74	0.93	1.97	0.45
Heat exhaustion	2.72	3.11	3.51	7.06	12.79	7.59
Other	1.04	2.28	4.07	6.69	11.02	4.47
	US Marine Corps					
Heatstroke	10.3	7.31	7.23	9.21	12.52	18.8
Heat exhaustion	34.75	34.47	40.41	51.18	81.5	75.21
Other	48.65	51.18	69.85	63.09	56.73	55.09
	US Air Force					
Heatstroke	1.11	1.08	0.76	0.71	2	1.33
Heat exhaustion	7.23	14.89	28.07	15.12	16.25	12.66
Other	3.89	12.19	18.46	16.07	10.68	7.77

*Includes the *International Classification of Diseases, Ninth Revision, Clinical Modification* (*ICD-9-CM*) codes 992.0–992.9, based on the hospitalization database, DoD Reportable Medical Events (RMES, NDRS, and AFRESS), and outpatient database. Reportable medical events data available since 1994, NDRS data available since 2001, and AFRESS data available since 2001. Outpatient data available since 1996. Rates are per 1,000 person-years.

DoD: Department of Defense

RMES: Reportable Medical Events System

NDRS: Naval Disease Reporting System

AFRESS: Air Force Reportable Events Surveillance System

Data source: Defense Medical Surveillance System, US Army Medical Surveillance Activity, US Army Center for Health Promotion and Preventive Medicine, April 27, 2004.

- Fort Sill, Oklahoma
- Fort Knox, Kentucky

US Marine Corps
- Parris Island, South Carolina
- San Diego, California

US Air Force
- San Antonio, Texas

The US Navy is the only exception; its single training base is located at Great Lakes Naval Training Center in Illinois. Characteristically, the highest training load occurs during the summer after most recruits finish school for the year. Between 1980 and 2002, 5,146 US Army soldiers were hospitalized with heatstroke.[1] During that period, there was a 60% reduction in hospitalization rates (probably because of fewer heat exhaustion cases) and a 5-fold increase in heatstroke hospitalizations (1.8 per 100,000 soldier-years in 1980 to 14.5 per 100,000 soldier-years in 2001).[1]

US military services reported a total of 6,725 initial heat-related injuries among newly accessioned personnel to the Defense Medical Surveillance System from 1998 through 2003 (rates for new officers are shown in Table 24-1). These diagnoses included records of hospitalizations, ambulatory visits, and reportable medical events with *International Classification of Diseases, Ninth Revision, Clinical Modification* (*ICD-9-CM*) codes indicative of heat-related illness (992.0–992.9). Incident cases were defined as the first diagnosis of heat-related injury per individual in a calendar year. Repeat events in the same calendar year were also included if they occurred 28 days or more after a previous diagnosis.

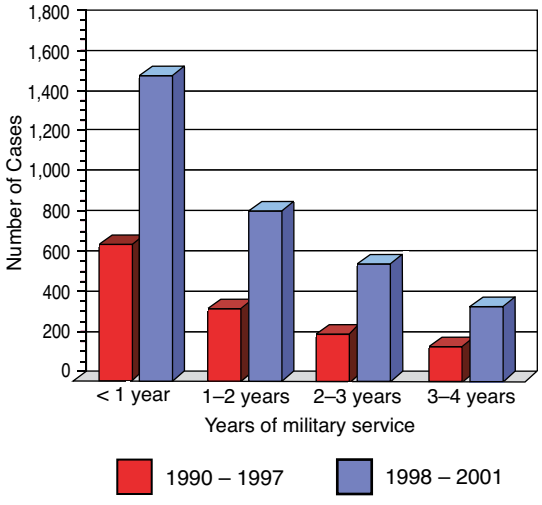

Fig. 24-1. Heat-related injuries among active US Army soldiers by length of service, 1990 through 2001. US Army soldiers experience fewer heat injuries as the number of years of service increases.
Reproduced from: US Army Medical Surveillance Activity, Defense Medical Surveillance System, Epidemiology and Disease Surveillance, US Army Center for Health Promotion and Preventive Medicine. Washington, DC: USACHPPM; 27 April 2004.

Incident rates of initial heat-related injuries for all Department of Defense recruits demonstrate a steady increase from 1998 through 2002. Some of the increases seen during this period may be because of the difference in how cases were identified as surveillance systems were modified. If the latter time frame is a better reflection of the true population data, it may also represent an increase in reported heat-related injuries as a result of a heightened awareness throughout the military medical community. Another contributor to an increase in heat injury cases may be more aggressive management of heat injuries earlier in their clinical courses. Recruit incident case rates for each of the armed services are shown in Table 24-2. Furthermore, consistent with recruit injuries, recent enrollment in the military has been identified as a specific risk factor for EHI.

A recent epidemiological study of nontraumatic deaths in US armed forces basic training from 1977 through 2001 demonstrated that one third of exercise-related recruit deaths attributed heat stress as a primary or secondary cause of death.[5] Forty-five percent of heat-related fatalities occurred in soldiers with sickle cell trait. Of the 5,146 Army soldiers who were hospitalized with heatstroke between 1980 and 2002, 37 died.[1] As length of service increased, the percentage of soldiers experiencing EHI decreased

TABLE 24-3

REPORTED OVERHYDRATION AND HYPONATREMIA RATES FOR NEW DOD RECRUITS, 1998–2003*

1998	1999	2000	2001	2002	2003
2.46	2.78	2.96	3.58	2.87	3.62

DoD: Department of Defense
*Rates are per 1,000 person-years. Includes the *International Classification of Diseases*, 9th Revision, Clinical Modification (ICD-9-CM) codes 276.1 or 276.1 and either 276.6 or 992.0–992.9.
Data source: Defense Medical Surveillance System, US Army Medical Surveillance Activity, US Army Center for Health Promotion and Preventive Medicine, 2004.

(Figure 24-1). In 2002, new Army recruits experienced 880 heat injuries, accounting for 48% of injuries Army-wide.

Another diagnosis associated with heat-related illness is that of hyponatremia caused by overhydration and salt depletion. Hyponatremia has a relatively low incidence rate (~ 1 case per 100,000 soldier-years),[1] but can occur in clusters.[6] There are several factors that make recruits prone to symptomatic hyponatremia, including poor heat acclimation, excessive water consumption, underconsumption of salt, and small body size. Among recruits at Fort Benning, Georgia, in 1997, there were five cases of hyponatremia attributed directly to excessive water consumption used to treat suspected dehydration, including one fatal case.[7] These events prompted revision of the water replacement guidelines to limit fluid intake to a maximum of 12 quarts daily; decrease the hourly requirements; and base hourly water intake and rest on the level of exertion, in addition to the heat category.[8] Table 24-3 shows the incident cases of hyponatremia and overhydration for Department of Defense recruits from 1998 through 2003.

PHYSIOLOGY AND PATHOPHYSIOLOGY

Humans normally regulate body (core) temperatures near 37°C. Small fluctuations within the narrow range of 35°C to 41°C can degrade exercise performance. Larger fluctuations outside of that range can be lethal.[9] Body temperature is maintained through two parallel processes: behavioral temperature regulation and physiological temperature regulation. Behavioral temperature regulation operates largely through conscious behavior and may use any means available. Physiological temperature regulation in warm environments operates through responses that do not depend on conscious voluntary behavior and includes control of the following: *(a)* rate of metabolic heat production, *(b)* heat flow via the blood from the core to the skin, and *(c)* sweating.

Physiological control systems can produce graded responses according to the disturbance in the regulated variable, in this case core temperature. Usually, the magnitude of changes in response (eg, sweating, skin blood flow) is proportional to displacement of the regulated variable (core temperature) from some basal value. Such control systems are known as proportional control systems. Both peripheral (skin) and core thermal receptors provide afferent input into the hypothalamic thermoregulatory center.[10]

Thermal receptors in the core and skin send information about their temperatures to a central integrator, located in the preoptic anterior hypothalamus.[11] This integrator generates a thermal command signal that participates in the control of sweating, skin vasodilation, and skin vasoconstriction. The concept of one thermal command signal is supported by data indicating that *(a)* the contributions of core and skin temperature inputs to changes in sweating and skin blood flow are the same; and *(b)* the thresholds for sweating and skin vasodilation are simultaneously shifted, and to a similar degree, by factors such as circadian rhythm, fever, menstrual cycle phase, and heat acclimation.

Physical exercise will cause a body temperature increase or hyperthermia.[10] This is because muscular contraction produces metabolic heat that is transferred from the active muscle to blood and the body core. Because skeletal muscle contraction is ~20% efficient, then ~80% of expended energy is released as heat, which needs to be dissipated from the body to avoid heat storage and increasing body temperature. Physiological adjustments occur that redirect blood flow from the body core to the periphery, thereby facilitating heat transfer from within the body to the skin, where it can be dissipated into the environment.

Heat exchange between the skin and the environment is governed by biophysical properties dictated by surrounding air or water temperature; air humidity; air or water motion; solar, sky, and ground radiation; and clothing. The biophysical avenues of this heat exchange are conduction, convection, radiation, and evaporation. The nonevaporative avenues (conduction, convection, and radiation) are often collectively called dry heat exchange. The energy balance equation describes these relationships between the body and environment:

$$S = M - (\pm W) \pm (R + C) \pm K - E,$$

where S = rate of body heat storage; M = rate of metabolic energy (heat) production; W = mechanical work, either concentric (positive) or eccentric (negative) exercise; R + C = rate of radiant and convective energy exchanges; K = rate of conduction (important only when in direct contact with an object [eg, clothing] or a substance [eg, water]); and E = rate of evaporative loss. The sum of these (= heat storage) represents heat gain if positive or heat loss if negative.

Heat acclimation results in biological adaptations that reduce the negative effects of heat stress. Heat acclimation occurs through repeated heat exposures

TABLE 24-4

ACTIONS OF HEAT ACCLIMATION*

Improved	Better Defended	Increased	Lowered	Reduced
Thermal comfort	Blood pressure	Stroke volume	Metabolic rate	Core body temperature
Sweating	Plasma (blood) volume	Total body water	Heart rate	Electrolyte loss (sweat and urine)
Earlier onset				
Higher rate	Plasma (blood) volume			
Redistribution (jungle)				
Hidromeiosis resistance (jungle)				
Skin blood flow				
Earlier onset				
Higher rate (jungle)				
Exercise performance				
Cardiovascular stability				
Myocardial compliance				
Fluid balance				
Thirst				
Intestinal blood flow during cutaneous vasodilation				

* During acclimation, cardiovascular stability is improved as heart rate is decreased and stroke volume is improved. The overall core body temperature is reduced. Sweating is improved as the eccrine glands are recruited, causing a higher sweat rate and more dilute sweat that allows the body to conserve electrolytes.

Adapted from: US Army Center for Health Promotion and Preventive Medicine. *Heat Stress Control and Heat Casualty Management*. Washington, DC: Headquarters, DA, DN, and DAF; 2003. TB Med507/AFPAM 48-152(I). Technical Bulletin. Available at: http://chppm-www.apgea.army.mil/heat/. Accessed January 12, 2006.

that are sufficiently stressful to elevate both core and skin temperatures and provoke profuse sweating. These biological adaptations occur from integrated changes in thermoregulatory control, fluid balance, and cardiovascular responses (Table 24-4). The magnitude of biological adaptations induced by heat acclimation depends largely on the intensity, duration, frequency, and number of heat exposures.[10] Exercise in the heat is the most effective method for developing heat acclimation; however, even resting in the heat results in limited acclimation. The full development of exercise-heat acclimation need not involve daily 24-hour exposure.

Heat acclimation mediates improved submaximal exercise performance by reducing body temperature and physiological strain. The three classical signs of heat acclimation are lower heart rate, lower core temperature, and higher sweat rate during exercise-heat stress. Skin temperature is often lower after heat acclimation than before, and thus dry heat loss is less (or, if the environment is warmer than the skin, dry heat gain is greater). To compensate for the changes in dry heat exchange, there must be an increase in evaporative heat loss to achieve heat balance. After acclimation, sweating starts earlier and at a lower core temperature (ie, the core temperature threshold for sweating is decreased). The sweat glands also become resistant to hidromeiosis and fatigue so that higher sweat rates can be sustained. Earlier and greater sweating improves evaporative cooling (if the climate allows evaporation) and reduces body heat storage and skin temperature. Lower skin temperatures will decrease the cutaneous blood flow required for heat balance (because of greater core-to-skin temperature gradient) and reduce cutaneous venous compliance so that blood volume is redistributed from the peripheral to the central circulation. All of these factors reduce cardiovascular strain and enhance exercise-heat performance.

Heat acclimation increases the sweat rate, which enhances evaporative cooling. Increased sweating requires additional water consumption. Acclimation also increases the ability of the body to conserve electrolytes. An unacclimated individual will lose a higher amount of salt while sweating. This explains why new recruits are particularly vulnerable to hyponatremia.

Acquired thermal tolerance refers to cellular adaptations from a severe nonlethal heat exposure that allows the organism to survive a subsequent and otherwise lethal heat exposure.[12,13] Acquired thermal tolerance and heat acclimation are complementary, as acclimation reduces heat strain and tolerance increases survivability to a given heat strain. For example, rodents with fully developed thermal tolerance can survive 60% more heat strain than what would have been initially lethal.[13] Thermal tolerance is associated with heat shock proteins (HSPs) binding to denatured or nascent cellular polypeptides. These proteins provide protection and accelerate repair from heat stress, ischemia, monocyte toxicity, and ultraviolet radiation in cultured cells and animals. HSPs are grouped into families based on their molecular mass. These HSP families have different cellular locations and functions that include processing stress-denatured proteins, managing protein fragments, maintaining structural proteins, and chaperoning proteins across cell membranes.

The HSP responses increase within several hours of the stress and last for several days after exposure. After the initial heat exposure, mRNA levels peak within an hour and subsequent HSP synthesis depends on both severity of heat stress and cumulative heat stress imposed.[13] Both passive heat exposure and physical exercise elicit HSP synthesis;[14] however, the combination of exercise and heat exposure elicits a greater HSP response than either stressor does independently.[15] In addition, HSP responses vary depending on specific tissue (eg, brain and liver tissue demonstrate greater responses then skeletal muscle tissue). It seems probable that other cellular systems also contribute to improved thermal tolerance.

RISK MANAGEMENT AND PREVENTION

Effective leadership and heat injury risk management can mitigate the risk of EHI. Heat injury hazards include high heat category and high exertion (especially on sequential days), poor acclimation, individual risk factors, and time (length of exposure and recovery time). The *Commander's, Senior NCO's, and Instructor's Guide to Risk Management of Heat Casualties*[16] is a detailed source on risk management, hot weather injuries/casualties, and medical considerations. This information is presented in a five-step format to:

1. identify hazards,
2. assess hazards,
3. develop controls,
4. implement controls, and
5. supervise and evaluate procedures and control measures.

Physical Fitness and Body Mass Index

Individuals with poor fitness have reduced heat tolerance. They take longer to acclimate, and they sweat less efficiently than fit soldiers. A case-control study of US Marine Corps recruits demonstrated that recruits with a 1.5 mile run time greater than 12 minutes had a higher risk (odds ratio of 3.4) of EHI.[4] This effect was further amplified by having an increased body mass index (Table 24-5). Recruits

TABLE 24-5

ODDS RATIO FOR DEVELOPING EXERTIONAL HEAT ILLNESS DURING US MARINE CORPS BASIC TRAINING, 1988–1992*

	1.5 Mile PFT1 Run Time		
BMI Category	**< 10 Min**	**10– < 12 Min**	**12+ Min**
< 22 kg/m^2	1.0	1.5	3.5
22– < 26 kg/m^2	1.6	2.0	8.5
26+ kg/m^2	3.7	3.3	8.8

BMI: body mass index
PFT1: pulmonary function test 1
*Odds ratios (95% confidence interval) combining PFT1 run time and BMI category for exertional heat illness in male marine recruits at the Marine Corps Recruiting Depot, Parris Island, SC. As body mass increases and fitness decreases, the risk of exertional heat illness increases.
Adapted with permission from: Gardner JW, Kark JA, Karnei K, et al. Risk factors predicting exertional heat illness in male Marine Corps recruits. *Med Sci Sports Exerc.* 1996;28:939–944.

with both poor fitness and body mass index greater than 26 have a 9-fold greater risk of heat injury.[17] This may be because fat tissue has a low specific heat content, and high body fat may be associated with poor fitness and not being heat acclimated.

Hydration and Nutrition

Soldiers performing exercise in hot climates will often incur body water deficits (hypohydration) of 2% to 8% of their body weight. These water deficits occur because of fluid nonavailability or a mismatch between thirst and sweat losses. Dehydration increases physiological strain, decreases exercise performance, and can mediate EHI.[18] Fluid replacement guidelines are critical for recruits who have not yet become skilled in water discipline. Commanders should ensure that fluid replacement guidelines and work/rest guidelines are followed (Table 24-6). The water required to replace sweating may exceed the body's ability to absorb fluid, which is about 1.5 quarts per hour. Soldiers should not be expected to drink more than this amount per hour; any remaining liquid must be consumed before and after exertion. Soldiers should limit water consumption to ~ 12 quarts per day. It is essential to ensure adequate hydration of all soldiers before any exercise or work.

A critical component of warm weather training events is water resupply. This is particularly challenging during events in which soldiers are dispersed over a large area (eg, land navigation). Instructors should place resupply points in areas where the soldiers will be present. Many units have experienced EHI problems when water resupply points were placed away from the normal lanes of traffic. Soldiers should carry as much water as possible when separated from approved sources of drinking water and have at least one full canteen in reserve. All participants should know when and where water resupply will be available. Soldiers can live longer without food than without water. Personal hydration system packs are an effective and convenient way to remove barriers to drinking. Units should make cool, flavored liquids accessible and provide enough time for drinking and eating.

Complete consumption of rations, including salt packets, will provide adequate salt intake. Units may consider appointing a meal monitor or using the buddy system to ensure that all recruits are eating adequately. Food should be salted liberally during warm weather training. Soldiers may have a few days of increased salt requirements on initial accession or on arrival at a training location in a warm environment; this is because sweat contains more sodium before heat acclimation. Units may consider

TABLE 24-6

FLUID REPLACEMENT AND WORK/REST GUIDELINES FOR WARM WEATHER TRAINING CONDITIONS*

		EASY WORK		MODERATE WORK		HARD WORK	
Heat Category	WBGT Index (°F)	Work/Rest	Water Intake (qt/h)	Work/Rest	Water Intake (qt/h)	Work/Rest	Water Intake (qt/h)
1	78–81.9	NL	1/2	NL	3/4	40/20 min	3/4
2	82–84.9	NL	1/2	50/10 min	3/4	30/30 min	1
3	85–87.9	NL	3/4	40/20 min	3/4	30/30 min	1
4	88–89.9	NL	3/4	30/30 min	3/4	20/40 min	1
5	> 90	50/10 min	1	20/40 min	1	10/50 min	1

WBGT: wet-bulb globe temperature

NL: no limit to work time per hour (up to 4 continuous hours)

*Applies to average size and heat-acclimated soldier wearing battle dress uniform in hot weather. This table refers to soldiers who have been acclimated for at least 2 weeks. The work/rest times and fluid replacement volumes will sustain performance and hydration for at least 4 hours of work in the specified heat category. Fluid needs can vary based on individual differences (± 1/4 qt/h) and exposure to full sun or full shade (± 1/4 qt/h). Easy work: eg, walking on a hard surface at 2.5 mph with less than a 30-lb load; weapon maintenance; markmanship training. Moderate work: eg, patrolling; walking in sand at 2.5 mph with no load; calisthenics. Hard work: eg, walking in sand at 2.5 mph with load; field assaults. Rest: minimal physical activity (sitting or standing), accomplished in shade if possible. **Caution:** hourly fluid intake should not exceed 1 1/2 qt. Daily fluid intake should not exceed 12 qt.

Adapted from: US Army Center for Health Promotion and Preventive Medicine. *Commander's, Senior NCO's and Instructor's Guide to Risk Managemen of Heat Casualty*. Washington, DC: Headquarters, DA, DN, and DAF; 2002. Available at: http://chppm-www.apgea.army.mil/heat/. Accessed January 12, 2006.

Fig. 24-2. The Ogden cord. This hydration monitoring system involves placement of a short piece of 550 cord (or a shoestring) to the collar buttonhole or ear protection case. As the day progresses, each recruit places one knot in the cord after each canteen is consumed. A pace count cord with twelve beads can also be used.

providing light rations (in addition to meals) during prolonged training events.

Recruits can monitor hydration status by noting the color and volume of urine. Dark yellow urine and infrequent urination indicate that fluid consumption should be increased. It is important to remove any barriers to hydration. One way to monitor hydration effectively is to tie an Ogden (550 cord or shoestring) or pace-count cord to a buttonhole (Figure 24-2). A knot is added to the cord each time that a canteen of water has been consumed during the day. This tracking system allows instructors to scan recruits quickly for inadequate hydration.

Carbohydrate and electrolyte beverages (also known as sports drinks) can be used if recruits train for more than 6 hours without consuming meals. For healthy soldiers, these beverages generally provide no advantage over water; however, they can enhance fluid consumption because of their flavor and reduce risk of hyponatremia by providing additional sodium. If meals have not been consumed for several hours, the carbohydrate in the sports beverages can provide an advantage over water when performing strenuous work in the heat.[19-21]

Water can be cooled by shading and insulating water buffaloes or by using small mobile chillers. Soldiers should be encouraged to drink water instead of splashing it on their skin, which is really wasted water. This action might briefly improve comfort level, but does little to sustain performance and avoid heat illness, particularly in humid environments.

Rest, Activity, and Uniform Modifications

Rest, activity, and uniform modifications—as well as recovery—are key to sustaining work performance and mitigating heat injury risk. Work/rest guidelines delineate the amount of rest needed for each heat category and level of exertion (see Table 24-6). During timed events, such as land navigation or road marches, a group time-out period can be utilized so that the rest period of all participants is standardized. During extreme warm weather training, the program must be modified daily. High-exertion activities should be started during predawn hours. The distance of events can be shortened to negate the effect of thermal stress. Instructors concerned about standardization of tasks should be reminded that a 5-mile run in heat category 5 is much more strenuous than that same event in heat category 3. Shortening the event or load only equalizes the event with the conditions encountered with less thermal stress.

Leaders must ensure that, whenever possible, formations are placed in shaded areas. In areas with little shade (eg, ranges), construction of overhead shelter can protect trainees considerably. During warm weather runs and marches, individuals in formations should be spaced at least an arm's length apart, or the use of formation abandoned. This wider spacing allows improved heat dissipation and prevents soldiers from gaining thermal load from nearby soldiers. Although hosing down formations is commonly practiced, leaders should keep in mind that this practice increases the incidence of fungal skin problems and friction injuries.

Sleeping in an air-conditioned environment for at least 4 hours has been shown to mitigate heat injury risk. The temperature of trainee barracks should be monitored daily to ensure adequate overnight cooling. Malfunctioning barracks air conditioning should be a high priority problem during warm weather. Utilization of fans to circulate the cool air improves removal of thermal energy during sleep/rest periods. Recruits should be encouraged to shower with cool water to improve conductive heat loss. In addition, simply having the recruits immerse their arms and legs in cool water can remove heat effectively and bring relief.

Uniform modification improves cooling. Whenever safe, Kevlar (EI DuPont de Nemours and Company, Wilmington, Del) headgear and body armor should be removed. Uniforms can be worn without the t-shirt. Pants can be worn unbloused, and footgear can be removed during rest breaks. Marches normally performed with a full rucksack should be done with minimal load during heat category 5. Care should be taken to keep exposed skin protected from sunburn.

Other Individual Risk Factors

Other individual risk factors include skin disease, concomitant disease and the use of certain medications, illicit drugs, and alcohol. Skin diseases (eg, sunburn, atopic dermatitis, and contact dermatitis) can impair sweating over the affected skin and predispose soldiers to heat injury. Sunburn should be prevented by the availability and use of sun block (alcohol-based block can contribute to clogged eccrine ducts), and soldiers should be protected from exposure by using protective clothing and adequate shelter. When skin disease affects more than 5% of the body surface area, an individual should be kept from significant heat strain until the skin has healed.

Many concomitant diseases increase heat injury risk. Type 2 diabetes contributes to impaired thermoregulation secondary to autonomic dysfunction.[10] Preceding illness was a risk factor in 17% to 18% of heatstroke victims.[22] Spinal cord injury also impairs thermoregulation, because autonomic dysfunction impairs sweat and cutaneous vasodilation.[23] In instances in which the injury is more proximal than T6, sympathetic nervous system activity is also impaired.

Some drugs and dietary supplements impair thermoregulation or increase risk of heat injury (Table 24-7).[24-27] Medications with anticholinergic properties (eg, atropine, tricyclic antidepressants, and antihistamines) impair sweating and cutaneous vasodilation. Anticholinergic poisoning can induce hyperthermia in the absence of exertion.[28] Many blood pressure medications contribute to dehydration and impaired cutaneous vasodilatation and sweating. Sympathomimetics (eg, cocaine, ecstasy, ephedra, and amphetamine) cause thermogenesis by altering levels of serotonin and dopamine in the hypothalamus. The cocaine-associated death rate has increased during heat waves. Club drugs (eg, 3,4-methylenedioxymethamphetamine, γ-hydroxybutyrate, rohypnol, and ketamine) all cause hyperthermia.[29-31] Neuroleptics and inhaled anesthetics alter dopamine levels, causing thermogenesis. Anticonvulsants such as topiramate and zonisamide can impair thermoregulation.[32-34]

SPECTRUM OF HEAT ILLNESS

Minor heat illnesses include heat tetany, heat cramps, heat syncope, and heat exhaustion. Major EHIs include exertional heat injury, exertional heatstroke, and exertional rhabdomyolysis. Diagnostic

TABLE 24-7

DRUGS THAT INTERFERE WITH THERMOREGULATION

Drug or Drug Class	Proposed Mechanism of Action
Anticholinergics (atropine)	Impaired sweating, impaired blood flow to skin
Antihistamines	Impaired sweating, impaired blood flow to skin
Gluthemide (doriden)	Impaired sweating
Phenothiazines (a class of antipsychotic drugs, including thorazine, stelazine, and trilafon)	Impaired sweating, (possibly) disturbed hypothalamic temperature regulation
Tricyclic antidepressants (eg, imipramine and anitriptyline)	Impaired sweating, increased motor activity and heat production
Amphetamines, cocaine, and ecstasy	Increased psychomotor activity, activated vascular endothelium
Ergogenic stimulants (eg, ephedrine/ephedra)	Increased heat production
Lithium	Nephrogenic diabetes insipidus and water loss
Diuretics	Salt depletion and dehydration
β-blockers (eg, propranolol and atenolol)	Reduced skin blood flow and reduced blood pressure
Ethanol	Diuresis, possible effects on intestinal permeability
Anticonvulsants (eg, topiramate and zonisamide)	Impaired thermoregulation

Adapted from: US Army Center for Health Promotion and Preventive Medicine. *Heat Stress Control and Heat Casualty Management*. Washington, DC: Headquarters, DA, DN, and DAF; 7 March 2003. TB Med507/AFPAM 48-1452(I). Technical Bulletin. Available at: http://chppm-www.apgea.army.mil/heat/. Accessed January 12, 2006.

categories of heat exhaustion, exertional heat injury, and exertional heatstroke have overlapping features and should be considered a continuum of illness.

Minor Heat Illnesses

Heat Tetany

Heat tetany probably results from hypocapnia secondary to hyperventilation by an individual after exposure to heat stress. This condition typically occurs before heat acclimation; symptoms include muscle spasm, perioral numbness, and tingling. Management is focused on removing individual stress and allowing breathing to return to normal.

Heat Cramps

Heat cramps are brief, recurrent, often agonizing cramps of the skeletal muscle of the limbs and trunk. Cramping in the individual is usually preceded by palpable or visible fasiculations lasting 2 to 3 minutes. This cramping is recurrent and may be precipitated by vigorous use of the involved muscle groups. Heat cramps occur often in salt-depleted individuals during recovery after a period of work or exercise in the heat. Smooth cardiac and diaphragm muscles are not involved and there are no systemic manifestations. Although the exact etiology of heat cramps is unknown, it is postulated that it involves intracellular calcium accumulation that stimulates actin-myosin to produce muscle contractions.

Usually, patients with heat cramps have significant sodium deficits. Salt replacement helps resolve cramps. Some physicians advocate oral administration of 0.05% to 0.1% salt solutions for the treatment of heat cramps; however, medical evidence does not indicate whether salt treatment is more effective than merely waiting for resolution of the problem. Electrolyte beverages should also be considered. Salt tablets should *not* be used as an oral salt source. The goal of treatment is relief of cramps, not replacement of salt, which takes longer and is best accomplished by ingestion of salted foods or fluid over many hours. No significant complications have been reported from heat cramps except local muscle soreness and perhaps local injury. An episode of heat cramps does not imply a predisposition to heat injury. Heat cramps are often seen in unacclimated individuals, and an attempt to determine the reason for the episode may assist the command in determining if other soldiers may be at risk. Liberal use of salted food should reduce the incidence of heat cramps in an at-risk population.

Heat Syncope

Heat syncope (sometimes referred to as parade syncope) is a temporary circulatory failure following pooling of blood in the peripheral veins and a subsequent reduction in diastolic filling of the right ventricle. Symptoms range from light-headedness to loss of consciousness. Heat syncope frequently occurs during prolonged standing and is typically associated with hot weather environments. This condition presents more frequently if standing still occurs after completing a vigorous activity. Core body temperature is not elevated unless the heat attack follows exercise, and the skin is usually wet and cool. Typically, recovery is rapid after a victim is able to sit or lay supine, even though it may take up to an hour for heart rate and blood pressure to stabilize.

A complete history and physical examination should be obtained to rule out more severe heat illness or other causes of syncope. Syncope during or after work in the heat can indicate heat exhaustion or exertional heat injury; simple syncope is not associated with amnesia or impaired mental status. Exertional syncope can be heat-related; however, previously undetected cardiac problems are a key consideration in new recruits.

Heat Exhaustion

Heat exhaustion is the most common form of heat casualty and is not associated with end-organ damage. Heat exhaustion occurs when the body cannot sustain the level of cardiac output necessary to meet the body's demand for skin blood flow for thermoregulation, muscle exercising, and vital organ supply. Some factors that contribute to this illness include the following: dehydration-mediated hypovolemia, hot skin maximizing skin blood flow and compliance, and perhaps failure of splanchnic vasoconstriction, which together limit venous return. Signs and symptoms of heat exhaustion include dizziness, nausea, malaise, hypotension, tachycardia, muscle cramps, and hyperventilation. Sweating persists and is often profuse. The distinction between heat exhaustion and more severe heat illness is important because of the difference in treatment and prognosis. Treatment of heat exhaustion must begin immediately to prevent progression. Rest, skin cooling, and rehydration alleviate the symptoms.

Management is focused primarily on correcting excessive cardiovascular demand and water-electrolyte depletion. Cooling and rest reduce cardiac load. Heavy clothing is removed, and the patient is rested in a shaded, ventilated space while active cooling is initiated. Water-electrolyte depletion is corrected by administering oral or parenteral fluids, being careful

to watch for signs of hyponatremia.[6,21,35] Heat exhaustion patients will improve rapidly with these measures. During this initial period of observation, the soldier should be under the supervision of the same combat lifesaver or medic. Frequent changes of observers can contribute to a poor outcome. Individuals who do not improve or get worse should be evacuated immediately to the next level of medical care. Soldiers who improve should be evaluated by a healthcare specialist before their return to duty.

Physiologically, these patients retain the ability to thermoregulate if removed from heat stress. Despite this, active cooling to a core temperature of 101°F (38.3°C) is recommended for the following reasons:

- Skin vasoconstriction with active cooling rapidly reduces circulatory demand and improves venous return.
- Casualties with an as-yet unrecognized exertional heat injury or heatstroke not actively cooled will continue to have a rise in core temperature and sustain continued damage.

Because these conditions may initially be hard to distinguish, medical personnel may delay active cooling in patients who require it and are likely to progress to a more serious illness if not cooled promptly.

When medical aid is available, rectal temperature should be monitored at least every 15 minutes to ensure that core body temperature is falling to normothermic levels. Despite the convenience of oral or ear temperature measurement, these methods do not adequately assess core body temperature, and they should be discouraged. Any loss of consciousness or mental status changes should prompt the evaluation for EHI or exertional heatstroke. Patients should be reassessed frequently with checks of mental status, core body temperature, and fluid monitoring.

Patients with heat exhaustion recover rapidly. Young, healthy individuals can be appropriately managed in the field. Those patients who recover fully in 1 hour and who require up to 2 liters of oral rehydration may return to light duty for the remainder of the day and return to full duty the next day. However, they must avoid repeat heat stress exposure for at least 24 hours. These patients do not require further medical evaluation. Patients who do not recover fully within 1 hour or who require more than 2 liters of oral rehydration should be evaluated at the next level of care.[8,19-21]

A single episode of heat exhaustion does not imply any predisposition to heat injury. However, victims of more serious heat injuries may have decreased heat tolerance. Therefore, repeat episodes should prompt further evaluation.[36,37]

Exertional Heat Injury

Exertional heat injury represents the continuum between heat exhaustion and exertional heatstroke. There is no consensus on diagnostic criteria for distinguishing exertional heat injury from heat exhaustion or heatstroke. Therefore, close monitoring of vital signs and serum chemistries is essential, because early in the course of illness clinical symptoms might not reflect the underlying metabolic abnormalities.[38] Patients with exertional heat injury show evidence of organ/tissue injury or organ/tissue dysfunction; however, these patients do not display sufficient neurological abnormalities to meet the criteria for heatstroke. Other manifestations include elevated core body temperature and metabolic acidosis.

Organ dysfunction or tissue damage might not manifest early in exertional heat injury; therefore, during initial management, it might be difficult to distinguish from heat exhaustion by clinical symptoms alone. Consequently, all patients with suspected EHI should be thoroughly evaluated for organ damage before release, and a reevaluation is required the following day. Initial treatment includes active cooling to a core body temperature of 101°F (38.3°C). One study[39] showed that cooling within 40 minutes is associated with no mortality. If responders immediately initiate active cooling in the field, organ damage will be attenuated.[40]

Heatstroke

Pathophysiology

Heatstroke is characterized by elevated core body temperature greater than 104° F or 40°C (or lower if cooling has been initiated prior to determination of core body temperature) and CNS dysfunction resulting in delirium, convulsions, or coma. Heatstroke is a medical emergency. When the body is subjected to thermal stress, cutaneous vasodilation and dehydration from evaporative fluid loss shunt blood flow from the enteric mucosa. If thermal stress is persistent or dehydration is excessive, mucosal damage occurs. The resulting mucosal damage causes endotoxin release into the vasculature. Endotoxin is a powerful activator of proinflammatory cytokines, such as interleukins, tumor necrosis factor, and interferon.[41] Elevated levels of proinflammatory cytokines have been demonstrated in patients with exertional heatstroke.[42] Cytokines also cause endothelial damage and the release of endothelin and other activators of the clotting cascade. In addition, cytokines can have a pyrogenic effect on the hypothalamus.[43]

Cytokines are implicated in the attenuation of HSPs.[44] These small proteins are activated when cells are stressed by heat, ethanol, and other harsh exposures.[45,46] Thermal stress under normal conditions induces the expression of HSPs, thus resulting in thermotolerance via enhanced cellular protection from apoptosis (gene-induced cellular destruction),[47,48] possibly by enhanced cutaneous vasodilation and cooling. Ongoing thermal

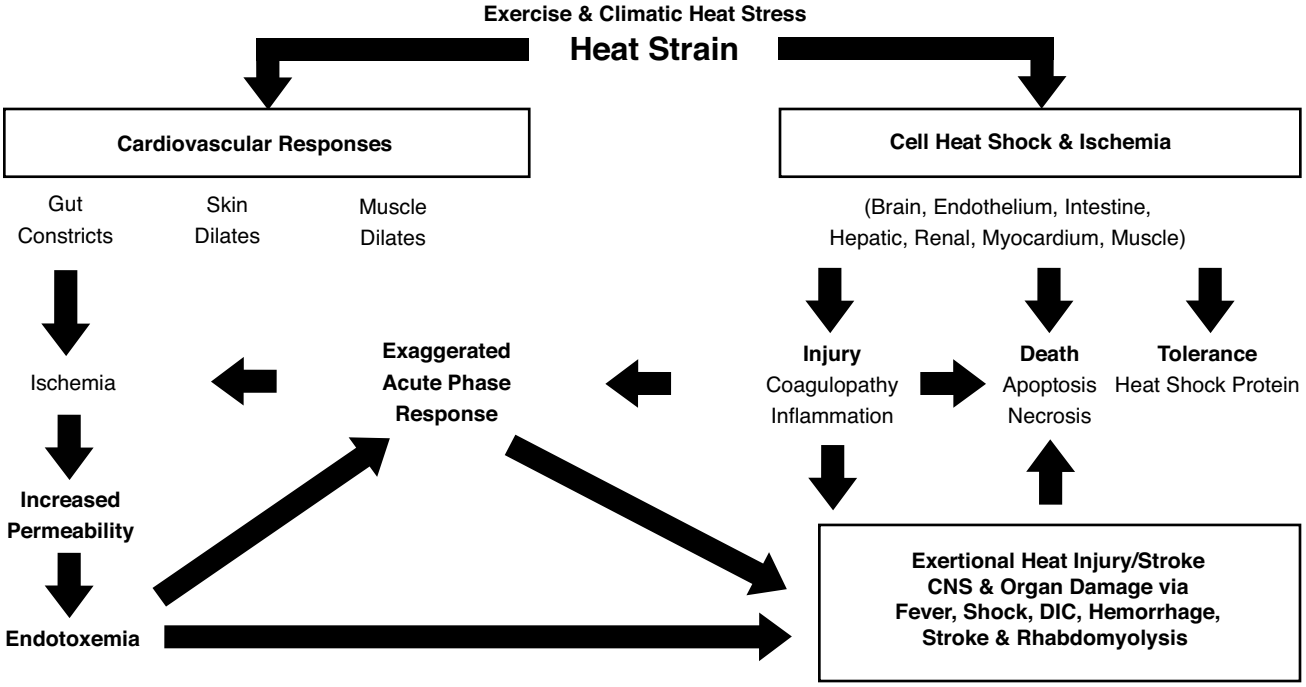

Fig. 24-3. Progression of heat strain to exertional heat illness/heatstroke.[1] Heatstroke is a medical emergency. When the body is subjected to thermal stress, cutaneous vasodilation and dehydration from evaporative fluid loss shunt blood flow from the enteric mucosa. If thermal stress is persistent or dehydration is excessive, mucosal damage occurs. The resulting mucosal damage causes endotoxin release into the vasculature. Endotoxin is a powerful activator of proinflammatory cytokines (eg, interleukins, tumor necrosis factor, and interferon). Elevated levels of proinflammatory cytokines have been demonstrated in patients with exertional heatstroke.[2] Cytokines cause endothelial damage and release endothelin and other activators of the clotting cascade. In addition, they have a pyrogenic effect on the hypothalamus.[3] Cytokines are also implicated in the attenuation of heatshock proteins.[4] These small proteins are activated when cells are stressed by heat, ethanol, and other harsh exposures.[5,6] Thermal stress under normal conditions induces the expression of heatshock proteins on cellular membranes resulting in thermotolerance via enhanced cellular protection from apoptosis (gene-induced cellular destruction),[1,7] possibly by enhanced cutaneous vasodilation and cooling. Ongoing thermal stress and inflammation after deactivation of heatshock proteins negate thermotolerance and can result in multiorgan failure if not reversed.
NO: nitric oxide
HSP: heatshock protein
CNS: central nervous system
DIC: disseminated intravascular congestion
(1) Sawka MN, Wenger CB, Pandolf, KB. Thermoregulatory responses to acute exercise—Heat stress and heat acclimation. In: Blatteis CM, Fregley MJ, eds. *Handbook of Physiology.* Section 4, *Environmental Physiology*. New York, NY: Oxford University Press, 1996: Chap 9. (2) Sakurada S, Hales JR. A role for gastrointestinal endotoxins in enhancement of heat tolerance by physical fitness. *J Appl Physiol*. 1998;84:207–214. (3) 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*. 2004;96:1943–1953.(4) Snoeckx LH, Cornelussen RN, Van Nieuwenhoven FA, Reneman RS, Van Der Vusse GJ. Heat shock proteins and cardiovascular pathophysiology. *Physiol Rev*. 2001;81:1461–1497. (5) Ang D, Liberek K, Skowyra D, Zylicz M, Georgopoulos C. Biological role and regulation of universally conserved heat shock proteins. *J Biol Chem*. 1991;266:24233–24236. (6) Simpson SA, Alexander DJ, Reed CJ. Heat shock protein 70 in the rat nasal cavity: Localisation and response to hyperthermia. *Arch Toxicol*. 2004;78:344–350. (7) DeFranco DB, Ho L, Falke E, Callaway CW. Small molecule activators of the heat shock response and neuroprotection from stroke. *Curr Atheroscler Rep*. 2004;6:295–300.

stress and inflammation after deactivation of HSPs negates thermotolerance and can result in multiorgan failure if not reversed. Figure 24-3 provides a diagram of the possible progression of heat strain to exertional heat injury/stroke.[10] Hyperthermia and cardiovascular responses to exercise-heat stress can result in reduced perfusion of the intestine and other body tissues, thus resulting in ischemia and excessively high tissue temperatures (heat shock, > 41°C). The magnitude and duration of the heat shock will influence whether the cell responds by adaptation (acquired thermal tolerance), injury, or death (apoptotic or necrotic). This can result in a variety of systemic coagulation and inflammatory responses.[49] It is suspected that the inflammatory response is primed (eg, leukocytosis, expression of proinflammatory cytokines) so that a subsequent severe exercise-heat exposure induces an accentuated acute phase response. This exaggerated acute phase response could mediate fever (in addition to exercise hyperthermia) and/or enhance the likelihood of tissue injury and cellular death.

The severity of heat injury is often not apparent on initial presentation. Individuals performing or competing in strenuous activities in hot weather who exhibit symptoms of serious exertional heat illness (eg, unsteady gait, sweaty and flushed skin, dizziness, headache, tachycardia, paresthesias, weakness, nausea, and cramps) should be immediately evaluated for their mental status, core (rectal) temperature, and vital signs. Poor or worsening mental status (ataxia and confusion) represents a true medical emergency, and these individuals need rapid intervention and evacuation to a medical treatment facility.

Forms of Heatstroke

There are two forms heatstroke that occur under different settings and produce different clinical pictures. Exertional heatstroke occurs in physically active persons who are producing substantial metabolic heat loads during sports, military training, or physical labor. Classic heatstroke is most common in the elderly and in young children who have impaired thermoregulation as a result of illness or medication. Often, it presents as an epidemic during urban heat waves. During the 2003 heat wave in Europe, 14,800 excess deaths were attributable to classic heatstroke in France alone.[50] One clinically important difference is that exertional heatstroke is more often complicated by rhabdomyolysis.

If these criteria are strictly adhered to, exertional heatstroke would be underdiagnosed, because coma, convulsions, and cessation of sweating may occur late in the presentation. However, cessation of sweating is rarely seen with exertional heatstroke. Moreover, patients who receive immediate rapid cooling might have a reduced core body temperature upon arrival of medical aid with normalized mental status, as well as minimal organ damage.[40,51] Thus, a history of significant amnesia and/or mental status changes (eg, combativeness and confusion) should alert the provider to diagnose heatstroke. Heatstroke can be complicated by systemic inflammatory response syndrome (SIRS), shock, and multiorgan dysfunction syndrome including arrhythmia, rhabdomyolysis, acute renal and hepatic failure, and disseminated intravascular coagulation.[52-54]

Central Nervous System Dysfunction

The development of CNS dysfunction during heatstroke is partially because of metabolic derangements and cerebral ischemia secondary to vasoconstriction of the carotid artery[55] and other cerebral blood vessels.[56] The cerebellum is the most thermosensitive area of the brain. Soldiers who are developing heatstroke often have ataxia or dysarthria prior to the development of mental status changes. Focal CNS lesions seen after recovery are cerebellar specific, and ataxia and dysarthria may persist.[51]

Exertional Rhabdomyolysis

Exertional rhabdomyolosis—which may occur without elevations in core body temperature or encephalopathy in new recruits who engage in strenuous activity for the first time—may occur as a complication of exertional heatstroke. Exertional rhabdomyolysis is caused by skeletal muscle damage with release of cellular contents into blood circulation. During muscle contraction, adenosine triphosphate (ATP) drives the contraction of actin and myosin myofilaments. Increased muscle metabolism associated with exercise and heat contributes to the development of an increase in intracellular calcium that impairs ATP production. On inhibition of ATP production, ATP-dependent proteolysis and cytokine release induce apoptosis of myocyte cells.[57]

Rhabdomyolysis can vary from asymptomatic elevations of skeletal muscle creatine phosphokinase (CPK) to muscle pain, weakness, and tenderness with associated myoglobinuria. A specific CPK level cannot define exertional rhabdomyolysis, but CPK is the most sensitive test for its presence. Exercising trainees frequently develop CPK levels ranging from 500 to 1,000 units per liter with no other clinical abnormalities, but seldom more than 3,000 units per liter in the absence of exertional heat injury. Myoglobin has a low molecular weight, and the kidney clears it from plasma in 1 to 6 hours.[57,58] During the myoglobinuric

phase, urine appears brownish red. In the absence of urine discoloration, a urine dipstick may be tested for blood. If positive, and no red blood cells are present on microscopic analysis, myoglobinuria is highly likely. Laboratory measurement of urine myoglobin can be done for confirmation. Because myoglobinuria is transient, evaluation may fail to detect the presence of myoglobin, particularly if presentation for medical care is delayed. Myoglobin is cleared through the renal glomeruli. When urine pH is less than 5.6, myoglobin is broken down into globulin and ferrihemate, which is extremely nephrotoxic.[59] A negative myoglobin test does not rule out rhabdomyolysis.

CPK, which has a higher molecular weight, usually peaks at 24 to 36 hours and then decreases 39% daily. If a second-wave phenomenon occurs and CPK levels start rising after the initial peak, an increase in muscle damage is occurring, and compartment syndrome should be suspected.[58] Compartment syndrome can be an insidious complication of exertional rhabdomyolysis. Care should be taken to fully evaluate any complaints of localized severe muscle pain, swelling, or distal parasthesias. Pain with passive stretch is the most sensitive test for compartment syndrome. Loss of distal pulses is a late finding in compartment syndrome.[60] See also Chapter 10, Rhabdomyolysis and Compartment Syndrome in Military Trainees.

Cardiovascular Findings

Patients with heatstroke will exhibit a hyperdynamic circulatory state. Sinus tachycardia and increased cardiac strain are common findings. Electrocardiogram findings may include ST-wave segment depression, T-wave abnormalities, and conduction disturbances. During the acute phase of heatstroke, patients are susceptible to thermal-induced arrhythmia and inflammatory myocardial damage. During the recovery phase of exertional heatstroke, hyperkalemia can contribute to arrhythmia. Epidemiological data of marine recruit deaths at Parris Island suggest that individuals with exertional heatstroke have a 3,000-fold higher risk of sudden cardiac death than those without exertional heatstroke.[61] Exertional heatstroke should be considered in all cases of sudden cardiac death during exercise in recruit populations. It is possible that hearts with proarrhythmic conditions (eg, Brugada syndrome and long QT syndrome) have increased sensitivity to thermal and sympathetic input.[62,63]

Liver Problems

Hepatic injury is generally observed early in heatstroke patients.[64] The liver is a major source of inflammatory mediators and has the largest population of macrophages in the body, and is thus more sensitive to activation of these cytokines. There are two phases of SIRS-associated liver failure. The first phase involves hepatic damage that is seen immediately after heatstroke. This phase is most likely a result of thermal stress and circulatory disturbances and is also referred to as primary hepatic dysfunction/failure. Because the liver uses 25% of cardiac output at rest, shunting of the blood to the peripheral circulation has the greatest impact on this organ.[65] Patients with initial hepatic dysfunction after exertional heatstroke often have mild elevations of transaminases, elevated lactate dehydrogenase levels,[66] and mild biliary cholestasis (serum total bilirubin: 1.4–2.0 mg/dL). Patients may develop transaminase levels of 100 or more times the upper limit of normal and subsequently develop disseminated intravascular coagulation, elevated lactate levels, and hypoglycemia (secondary to impaired gluconeogenesis). As patients enter this secondary phase, hepatic dysfunction is exacerbated by the effect of inflammatory mediators on the liver itself. Management includes maintenance of euglycemia and careful monitoring of fluids and electrolytes.

Fulminant hepatic failure develops rarely and is associated with high mortality in recovering patients with heatstroke. Development of new mental status changes several days after exertional heatstroke in a patient with severe liver dysfunction heralds the onset of fulminant hepatic failure.[67] During the first stage of hepatic encephalopathy, these symptoms may be very subtle, encompassing insomnia, changes in affect, euphoria, or slurred speech.

Concomitant renal failure is a poor prognostic sign.[68] Any patient who displays early encephalopathy, worsening coagulation abnormalities, or infection should be transferred to a transplant center where hepatologists can direct management. There are multiple reports of recovery of liver function in patients who are managed conservatively.[64] Recently, a liver transplant has been offered, but there are no reported cases of long-term survival after transplantation.[69,70]

Kidney Problems

Acute renal dysfunction (creatinine > 2.0 mg/dL without the need for dialysis) is commonly seen in heatstroke. The kidney is vulnerable to heat stress because of the damage to both the renal tubule and the renal vasculature.[71] Patients with a CPK value greater than 10,000 to 16,000 IU/L are more likely to develop acute renal dysfunction.[71] When lower CPK values are present, this acute renal dysfunction may be more likely secondary to sympathoadrenal

activation, cytokine production, and endothelial damage. Hypotension, acidosis, myoglobinuria, disseminated intravascular coagulation, and decreased renal blood flow are associated with the development of oliguric acute renal failure (urine output < 400 mL/24 h).[72] Urine examination may reveal pyuria, proteinuria, microscopic hematuria, and granular casts.

Systemic Inflammatory Response Syndrome

SIRS was initially described by the American College of Chest Surgeons.[73,74] The diagnostic criteria for SIRS are listed in Table 24-8. A normally functioning immune system consists of a balance of complex interactions among cellular mediators, cytokines, stress hormones, and cellular defense mechanisms that target local areas of disease. If this balance is disturbed by a significant stress (eg, endotoxemia, hyperthermia, or trauma), the immune system can become so systemically activated that the organism's own healthy cells are attacked throughout the body. This causes further inflammation, causing additional self-destructive actions.[54] SIRS is a hypermetabolic, hyperadrenergic state that can lead to multiorgan dysfunction syndrome, shock, and death.

The body's response to heat stress is very similar to the model of sepsis.[75] Exercise dominates the sympathetic adrenal nervous system. Thermal stress-induced cytokines and histamine further increase autonomic activity and the adrenal surge of glucocorticoids.[76] Sudden depletion of adrenal reserve (particularly cortisol) may account for vascular collapse and shock.[77] Septic shock is believed to have two phases: (1) an initial hyperinflammatory phase and (2) a hypoinflammatory phase and shock.[78] Recent research points to a relative adrenal/cortisol deficiency as a mediator of shock in patients with SIRS.[77]

TABLE 24-8

DIAGNOSTIC CRITERIA* FOR SYSTEMIC INFLAMMATORY RESPONSE SYNDROME

Criteria	Values
Temperature	> 38°C or < 36°C
Heart rate	> 90/min
Respiratory rate or	> 20 min
$Paco_2$	< 32 mm Hg
Leukocyte count	> 12,000/mm^3 or < 4,000/mm^3 or > 10% bands

$Paco_2$: partial pressure of carbon dioxide, arterial

* Must meet two or more criteria for diagnosis of systemic inflammatory response syndrome.

Data source: Bone RC, Balk RA, Cerra FB, et al. Definitions for sepsis and organ failure and guidelines for the use of innovative therapies in sepsis. The ACCP/SCCM Consensus Conference Committee. American College of Chest Physicians/Society of Critical Care Medicine. *Chest.* 1992;101:1644–1655.

Coagulopathy

Inflammation activates endothelial cells, which in turn activate coagulation and fibrinolytic pathways.[79,80] Coagulation abnormalities can be manifested by heparin sensitivity, abnormalities of prothrombin consumption, thromboplastin generation, clotting time, and clot retraction. Coagulopathy may be potentiated by hepatocyte damage, rhabdomyolysis, and possibly thermal activation of fibrinolysis.[49] Hepatic dysfunction and thermal injury to megakaryocytes slow the repletion of clotting factors. Platelet counts are usually low and so are levels of factor V and VIII. Abnormal hemostasis is manifested clinically by purpura, conjunctival hemorrhages, hemoptysis, hematuria, and neurological findings as a result of CNS hemorrhage.

Fluid and Electrolyte Imbalances

Dehydration as evidenced by hypovolemia and hypermosolality often contributes to high core body temperature that typically occurs with heatstroke.[18] In addition, in hot weather, dehydration reduces physical and mental work capabilities. Water depletion dehydration develops from sweat rates in excess of water replacement. Although loss of water occurs both from intracellular and extracellular fluids, extracellular contraction is often rapid and can evolve quickly. Salt depletion dehydration usually develops over several days, so extracellular fluid contraction is gradual, and symptoms develop slowly. Because salt depletion does not produce hypertonicity, thirst may not be as prominent. Muscle cramps sometimes accompany sodium depletion. Potassium depletion commonly accompanies salt depletion because of diminished intake and mineralocorticoid-driven kaliuresis, but actual hypokalemia is uncommon.

Hyponatremia refers to blood sodium below 130 mEq/L. In published cases of symptomatic exertional hyponatremia, serum sodium concentrations at presentation averaged 121 mEq/L and ranged from 109 to 131 mEq/L. Hyponatremia is associated with prolonged physical work (> 6 hours) and arises from fluid overload, underreplacement of sodium losses, or

a combination of both. The reduction of extracellular fluid solute leads to osmosis of water into the intracellular space. If intracellular swelling is of sufficient magnitude, symptoms of CNS dysfunction, lung congestion, and muscle weakness can occur.

Hyponatremia and dehydration-mediated heat exhaustion share many symptoms, and laboratory tests are necessary to distinguish the two disorders. Therefore, the initial treatment of patients who actually have mild hyponatremia is likely to have been administration of oral fluids, on the presumption that they were suffering from water-depletion heat exhaustion. Patients with water-depletion heat exhaustion respond quickly to fluid replacement, whereas hyponatremia is aggravated by administering hypotonic fluids and may progress to life-threatening cerebral edema. If a patient who is presumed to have heat exhaustion does not improve quickly in response to the administration of hypotonic fluids, such treatment should be discontinued and the patient should be evacuated. Repeated emesis is more often seen with hyponatremia. Therefore, if the patient has two episodes of emesis with a general deterioration, the patient should be evacuated for further medical evaluation.[6,81]

CLINICAL MANAGEMENT

Rapid Cooling

The clinical outcome of patients with heatstroke is principally a function of the magnitude and duration of body temperature (core and skin) elevation. The most important therapeutic measure is rapid reduction of body temperature elevation. Rapid cooling can reduce heatstroke mortality from 50% to 5%. One study[82] demonstrated that cooling patients to a normal core body temperature within 40 minutes is associated with significantly improved morbidity and mortality. Mental status changes in a trainee in the appropriate environment should always be treated as heatstroke. First responders should initiate rapid cooling immediately. Cooling should not be delayed while awaiting the arrival of medical personnel or awaiting a core body temperature. Victims must be evacuated quickly. Cooling and evaluation should proceed simultaneously, and core body temperature should be monitored closely.

The patient should lie down. Obtunded or comatose patients should be placed on their side with good airway management. Cooling should include the following steps:

- removing the outer layers of clothing,
- soaking the skin with water,
- using iced sheets, ice packs, or spray bottles,
- massaging the skin, and
- resoaking.

Care should be taken to avoid wetting the patient if he or she is pulseless and will require defibrillation.

Application of iced sheets and ice water immersion are the most effective methods of lowering body temperature. In addition, iced sheets are an effective cooling method for first responders. Coolers with ice-water–soaked sheets can easily be kept in all training areas. Patients tolerate the application of iced sheets well and often improve dramatically. Figure 24-4 illustrates the use of iced sheets. Fanning can accelerate cooling by enhancing convection. Application of water alone is not effective in humid environments. Rapid cooling of hyperthermic patients should continue until the rectal temperature reaches 101°F (38.3°C).

The following two invasive cooling techniques are *not* recommended: (1) ice water lavage and (2) enema/peritoneal lavage with cool fluids. These techniques do not provide faster cooling and have the additional disadvantages of potential complications and substantial inappropriate fluid loads.

Fig. 24-4. This cooling method involves the use of ice water-soaked sheets, which are maintained by instructors and stored in coolers at all training sites. When a recruit exhibits mental status changes, the outer layer of clothing is removed and the cold sheets are applied to all areas of exposed skin, as well as the top of the head.

Other First-Responder Actions

First responders should be prepared to provide basic life support and first aid. If transportation to an emergency medical facility will require more than 10 minutes, provisions should be made to administer advanced cardiac life support (including an automated external defibrillator). First responders and field medical teams must provide accurate clinical descriptions of the immediate events, symptoms, signs, vital signs, and mental status of the patient, along with training activities, environmental conditions, clothing, and treatment given before arrival at the medical facility. To avoid substantial treatment delay in settings with an increased risk of heat injuries, units should have at least one first responder trained in heat injury (with equipment, ice, communication, and a transport vehicle) on-site during strenuous hot weather training. Units should maintain automated external defibrillators in close proximity to high-exertion training areas.

Evacuation Criteria

All patients with mental status changes should be evacuated. Other symptoms that warrant immediate evacuation include repetitive vomiting, incontinence, and a core body temperature greater than 104°F (40°C) (Exhibit 24-1). Patients who do not meet evacuation criteria may be managed conservatively. Thirsty and alert patients can be given oral fluids (initial hour, using 1 quart per 30 minutes). Heat exhaustion patients generally recover rapidly with cooling and rehydration; however, those patients who fail to respond or worsen should be evacuated immediately to a medical facility. Figure 24-5 provides an algorithm for the field management of heat injury.

Conservative Field Management

Patients with intact CNS function respond well to oral rehydration therapy, which consists of resting in the shade and removing headgear, boots, and overblouse. Water and electrolyte beverages should

EXHIBIT 24-1

WARNING SIGNS AND SYMPTOMS OF EXERTIONAL HEAT ILLNESS AND IMMEDIATE ACTIONS

Common Signs/Symptoms	Immediate Actions
• Dizziness • Headache • Nausea • Unsteady walk • Weakness • Muscle cramps	• Remove from training • Allow casualty to rest in the shade • Give sips of water • While doing the above, call for medic evaluation of the soldier; medic will monitor temperature and check for mental confusion • If no medic is available, call for ambulance or medical evacuation
Serious Signs/Symptoms	**Immediately Call Medical Evacuation or Ambulance for Emergent Transport While Performing the Following:**
• Hot body, high temperature • Confusion/disorientation (mental status assessment) • Vomiting • Involuntary bowel movement • Convulsions • Weak or rapid pulse • Unresponsive, coma	• Have person lie down in shade with feet elevated until medical evacuation or ambulance arrives • Undress as much as possible • Pour cool water over the person and continue fanning the individual • Check for responsiveness, coma • Give *sips* of water if person is conscious • Monitor airway and breathing

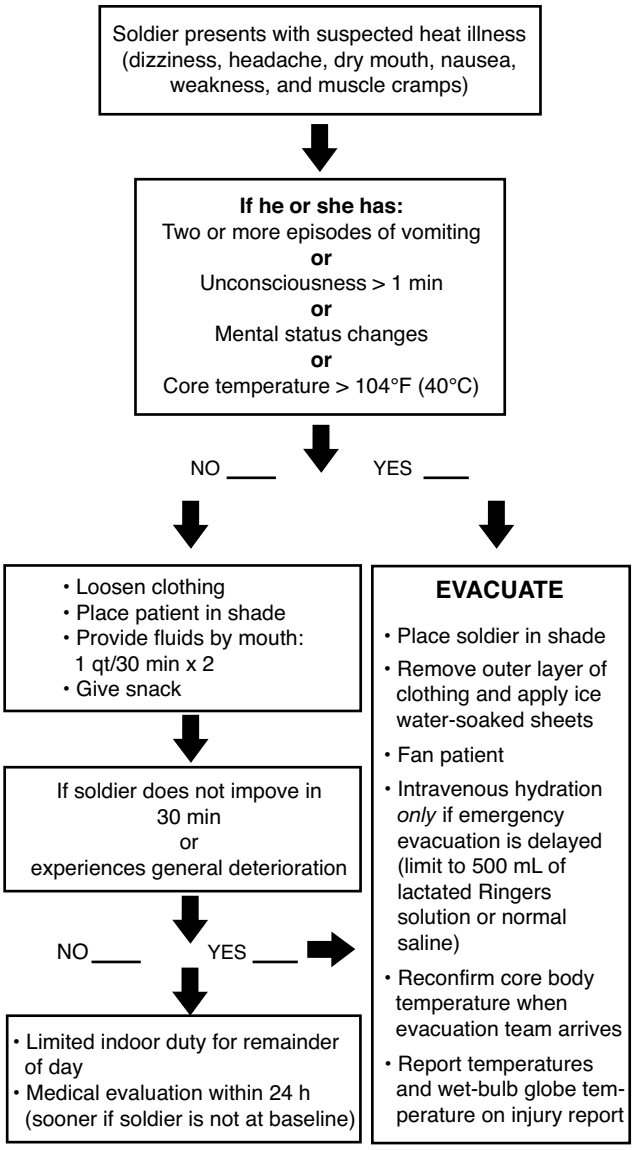

Fig. 24-5. Suggested algorithm for the field management of exertional heat illness.

be given orally for rehydration. Any soldier who has been managed conservatively should be evaluated by a medical provider before returning to full duty.

Management at the Medical Treatment Facility

Initial management at the medical treatment facility includes assessment of mental status, core body temperature and vital signs, intravenous access, cardiac monitoring, and oxygen. A finger-stick glucose test should be obtained to rule out hypoglycemia. Initial laboratory assessments should include a complete blood count, serum chemistry, renal panel, CPK, lactate dehydrogenase, liver-associated enzymes, and urinalysis for blood and red blood cells. If the initial laboratory test values are significantly abnormal, additional testing should include urine myoglobin, liver function, uric acid, and arterial blood gas.

Continued Care

Active cooling should be discontinued when core body temperature reaches 101°F (38.3°C) to avoid hypothermia from afterdrop. If attempts to cool the patient are successful, the core body temperature may rise again once cooling is stopped. Occasionally, cooling leads to shivering (a reponse to rapid heat removal), whereas the temperature is elevated; however, active cooling will remove more heat than is generated.

After cooling, continuing care is supportive and directed at complications of heatstroke as they appear. Patients with heatstroke frequently have impaired temperature regulation for several days, with alternate periods of hyperthermia and hypothermia. Constant monitoring is essential, and clinically significant deviations in temperature may require either cooling or warming measures. Body temperature changes may result from reasons other than hypothalamic instability (eg, infection). Given the hypermetabolic state exhibited by these patients, early attention to nutritional support should be initiated.[54]

Antipyretics should be avoided. Liver injury may be potentiated with acetaminophen, renal failure may worsen with nonsteroidal antiinflammatory drugs, and aspirin can depress platelet function and complicate disseminated intravascular coagulopathy. Chlorpromazine should not be used because it causes a relatively high incidence of hypotension in patients with serious heat illness. Lorazepam is probably the safest drug for sedation and control of shivering or seizures, in part because of it has low risk for hepatotoxcity and can be rapidly metabolized.

All patients with exertional heatstroke require cardiac monitoring until core body temperature and electrolyte imbalances are corrected. Any patient exhibiting dysfunction after successful cooling should be evaluated further with a computed tomography scan of the head.

Patients with exertional rhabdomyolysis require strict monitoring of urine output, urine pH, and serum pH. Urine output should be maintained at greater than 200 mL per hour, and urine pH should be between 6 and 7. This can be achieved with a forced alkaline diuresis using bicarbonate and mannitol.[60] If serum pH exceeds 7.5 or urine alkalinization is not attained, acetazolamide should be given. Furosemide

can also increase renal output. Animal studies have used the iron chelator desferrioxamine to prevent renal damage caused by the release of ferrihemate from myoglobin molecules.[60] If hyperuricemia is present, uricosuric agents may be helpful in patients with good urine output.[57] Dialysis may be required in some cases of progressive renal failure secondary to rhabdomyolysis.

Patients with suspected compartment syndrome should have intracompartmental pressure evaluated.[57] When the compartment pressure is 20 mm Hg below the diastolic pressure, or if pressures exceed 30 to 50 mm Hg, immediate fasciotomy should be considered.[58,60]

Patients with coagulopathy should be treated with fresh frozen plasma and platelets as indicated. Laboratory studies (prothrombin/partial thromboplastin time, platelet count, and fibrinogen) should be monitored.

After hospital discharge, soldiers should undergo a fitness-for-duty determination and should be profiled for a period of limited duty. Cases of exertional heatstroke should receive more extensive profiles, as delineated by service-specific regulations.

> Who paints those years, with all their scenes?—the hard-fought engagements—the defeats, plans, failures…—the long marches in summer—the hot sweat, and many a sunstroke, as on the rush to Gettysburg in '63—the night battles in the woods, as under Hooker at Chancellorsville—the camps in winter—the military prisons—the hospitals—(alas! alas! the hospitals).[83]
>
> — Walt Whitman
> *Prose Works* (1892)

SUMMARY

Because of the high risk of EHI experienced by new recruits, warm weather training continues to challenge commanders. Continued education of leaders on heat injury risk mitigation and initial field management of EHI can significantly reduce the incidence of severe EHI. High levels of vigilance in units may cause more cases of milder forms of EHI to be identified. Care should be taken to avoid discouraging leaders from identifying and treating milder injuries, because this approach often prevents more serious EHIs.

Risk mitigation is accomplished at the unit level by modification of the training schedule to avoid successive high-exertion activities and to conduct high-exertion activities during cooler hours. Modification of training conditions can also be accomplished through removing headgear and t-shirts, spacing formations widely, decreasing distance and speed of events, and providing well-cooled sleeping areas and classrooms. Individual risk factor modification includes identifying recruits who are ill, taking medications, or are poorly conditioned or overweight.

EHI represents a broad spectrum of illness that includes components of poor cardiac output, inflammation, and impaired thermoregulation. Exertional heatstroke is diagnosed when mental status changes are present. Rapid cooling of any patient with suspected exertional heatstroke is critical. Additional management includes evacuation to a medical treatment facility, where cardiac monitoring, electrolyte evaluation, and monitory of renal and liver functions can be accomplished. Policies for control and management of heat injuries can be found in the US Army technical medical bulletin, *Heat Stress Control and Heat Casualty Management*.[84]

REFERENCES

1. Carter RI, Cheuvront SN, Williams JO, et al. Hospitalizations and death from heat illness in US Army soldiers, 1980–2002. *JAMA*. In press.

2. US Army Center for Health Promotion and Preventive Medicine. Heat-associated injuries, US Army, 1990–2001. *Med Surveillance Monthly Rept*. 2002;8:2–11.

3. US Army Center for Health Promotion and Preventive Medicine. Reportable medical events, US Armed Forces, 2002. *Med Surveillance Monthly Rept*. 2002;9:21–22, 26–28.

4. Kark JA, Burr PQ, Wenger CB, Gastaldo E, Gardner JWQ. Exertional heat illness in Marine Corps recruit training. *Aviat Space Environ Med*. 1996;67:354–360.

5. Scoville SL, Gardner JW, Magill AJ, Potter RN, Kark JA. Nontraumatic deaths during U.S. Armed Forces basic training, 1977–2001. *Am J Prev Med*. 2004;26:205–212.

6. O'Brien KK, Montain SJ, Corr WP, Sawka MN, Knapik JJ, Craig SC. Hyponatremia associated with overhydration in US Army trainees. *Mil Med.* 2001;166:405–410.

7. Craig SC, Knapik JJ, Brundage JH, et al. *Overhydration with Secondary Hyponatremia.* Aberdeen Proving Ground, Md: US Army Center for Health Promotion and Preventive Medicine; 1997.

8. Montain SJ, Latzka WA, Sawka MN. Fluid replacement recommendations for training in hot weather. *Mil Med.* 1999;164:502–508.

9. Katschinski DM. On heat and cells and proteins. *News Physiol Sci.* 2004;19:11–15.

10. Sawka MN, Wenger CB, Pandolf KB. Thermoregulatory responses to acute exercise-heat stress and heat acclimation. In: Fregley JM, Blatteis CM, eds. *Handbook of Physiology*. New York, NY: Oxford University Press; 1996: 157–185.

11. Boulant JA. Hypothalamic mechanisms in thermoregulation. *Fed Proc*. 1981;40:2843–2850.

12. Moseley PL. Heat shock proteins and heat adaptation of the whole organism. *J Appl Physiol*. 1997;83:1413–1417.

13. Maloyan A, Palmon A, Horowitz M. Heat acclimation increases the basal HSP72 level and alters its production dynamics during heat stress. *Am J Physiol*. 1999;276:R1506–R1515.

14. Febbraio MA. Does muscle function and metabolism affect exercise performance in the heat? *Exerc Sport Sci Rev*. 2000;28:171–176.

15. Skidmore R, Gutierrez JA, Guerriero V Jr, Kregel KC. HSP70 induction during exercise and heat stress in rats: Role of internal temperature. *Am J Physiol.* 1995:268:R92–R97.

16. US Army Center for Health Promotion and Preventive Medicine. *Commander's, Senior NCO's, and Instructor's Guide to Risk Management of Heat Casualties*. Washington, DC: Headquarters, DA, DN, and DAF; 2002. Available at: http://chppm-www.apgea.army.mil/heat/. Accessed December 26, 2005.

17. Gardner JW, Kark JA, Karnei K, et al. Risk factors predicting exertional heat illness in male Marine Corps recruits. *Med Sci Sports Exerc*. 1996;28:939–944.

18. Sawka MN, Coyle EF. Influence of body water and blood volume on thermoregulation and exercise performance in the heat. In: Hollozsy JO, ed. *Exercise and Sport Sciences Reviews.* Baltimore, Md: Williams & Wilkins; 1999: 167–218.

19. Sawka MN, Montain SJ. Fluid and electrolyte supplementation for exercise heat stress. *Am J Clin Nutr*. 2000;72(2 suppl):564S–572S.

20. Sawka MN, Montain SJ, Latzka WA. Hydration effects on thermoregulation and performance in the heat. *Comp Biochem Physiol A Mol Integr Physiol.* 2001;128:679–690.

21. Sawka MN, Greenleaf JE. Current concepts concerning thirst, dehydration, and fluid replacement: Overview. *Med Sci Sports Exerc.* 1992;24:643–644.

22. Epstein Y, Moran DS, Shapiro Y, Sohar E, Shemer J. Exertional heat stroke: A case series. *Med Sci Sports Exerc.* 1999;31:224–228.

23. Hagobian TA, Jacobs KA, Kiratli BJ, Friedlander AL. Foot cooling reduces exercise-induced hyperthermia in men with spinal cord injury. *Med Sci Sports Exerc.* 2004;36:411–417.

24. Epstein Y, Shani Y, Moran DS, Shapiro Y. Exertional heat stroke: The prevention of a medical emergency. *J Basic Clin Physiol Pharmacol.* 2000;11:395–401.

25. Krueger-Kalinski MA, Schriger DL, Friedman L, Votey SR. Identification of risk factors for exertional heat-related illnesses in long-distance cyclists: Experience from the California AIDS ride. *Wilderness Environ Med*. 2001;12:81–85.

26. Watson JD, Ferguson C, Hinds CJ, Skinner R, Coakley JH. Exertional heat stroke induced by amphetamine analogues. Does dantrolene have a place? *Anaesthesia*. 1993;48:1057–1060.

27. Martinez M, Devenport L, Saussy J, Martinez J. Drug-associated heat stroke. *South Med J*. 2002;95:799–802.

28. Christensen RC. Screening for anticholinergic abuse in patients with chronic mental illness. *Am J Emerg Med.* 2003;21:508.

29. Gahlinger PM. Club drugs: MDMA, gamma-hydroxybutyrate (GHB), rohypnol, and ketamine. *Am Fam Phys.* 2004;69:2619–2626.

30. Cole JC, Sumnall HR. The pre-clinical behavioural pharmacology of 3,4-methylenedioxymethamphetamine (MDMA). *Neurosci Biobehav Rev.* 2003;27:199–217.

31. Larsen PJ, Vrang N, Tang-Christensen M, et al. Ups and downs for neuropeptides in body weight homeostasis: Pharmacological potential of cocaine amphetamine regulated transcript and pre-proglucagon-derived peptides. *Eur J Pharmacol.* 2002;440:159–172.

32. Ben-Zeev B, Watemberg N, Augarten A, et al. Oligohydrosis and hyperthermia: Pilot study of a novel topiramate adverse effect. *J Child Neurol.* 2003;18:254–257.

33. Knudsen JF, Thambi LR, Kapcala LP, Racoosin JA. Oligohydrosis and fever in pediatric patients treated with zonisamide. *Pediatr Neurol.* 2003;28:184–189.

34. Cuddy MLF. The effects of drugs on thermoregulation. *AACN Clin Issues Adv Pract Acute Crit Care.* 2004;15:238–253.

35. Montain SJ, Sawka MN, Wenger CB. Hyponatremia associated with exercise: Risk factors and pathogenesis. *Exerc Sport Sci Rev.* 2001;29:113–117.

36. Porter AM. Collapse from exertional heat illness: Implications and subsequent decisions. *Mil Med.* 2003;168:76–81.

37. Phinney LT, Gardner JW, Kark JA, Wenger CB. Long-term follow-up after exertional heat illness during recruit training. *Med Sci Sports Exerc*. 2001;33:1443–1448.

38. Gardner JW, Kark JA. Fatal rhabdomyolysis presenting as mild heat illness in military training. *Mil Med.* 1994;159: 160–163.

39. Gaffin SL, Gardner JW, Flinn SD. Cooling methods for heatstroke victims. *Ann Intern Med.* 2000;132:678.

40. O'Brien KK. Case studies of exertional heat injury/stroke in military populations. *Med Sci Sport Exerc.* 2003;35:S3.

41. Bouchama A, Parhar RS, el-Yazigi A, Sheth K, al-Sedairy S. Endotoxemia and release of tumor necrosis factor and interleukin 1 alpha in acute heatstroke. *J Appl Physiol.* 1991;70:2640–2644.

42. Lu KC, Wang JY, Lin SH, Chur P, Lin YF. Role of circulating cytokines and chemokines in exertional heatstroke. *Crit Care Med.* 2004;32:399-403.

43. Sakurada S, Hales JR. A role for gastrointestinal endotoxins in enhancement of heat tolerance by physical fitness. *J Appl Physiol*. 1998;84:207–214.

44. 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.* 2004;96:1943–1953.

45. Snoeckx LH, Cornelussen RN, Van Nieuwenhoven FA, Reneman RS, Van Der Vusse GJ. Heat shock proteins and cardiovascular pathophysiology. *Physiol Rev*. 2001;81:1461–1497.

46. Ang D, Liberek K, Skowyra D, Zylicz M, Georgopoulos C. Biological role and regulation of universally conserved heat shock proteins. *J Biol Chem*. 1991;266:24233–24236.

47. Simpson SA, Alexander DJ, Reed CJ. Heat shock protein 70 in the rat nasal cavity: Localisation and response to hyperthermia. *Arch Toxicol*. 2004;78:344–350.

48. DeFranco DB, Ho L, Falke E, Callaway CW. Small molecule activators of the heat shock response and neuroprotection from stroke. *Curr Atheroscler Rep*. 2004;6:295–300.

49. Bouchama A, Knochel JP. Heat stroke. *N Engl J Med*. 2002;346:1978–1988.

50. Dhainaut JF, Claessens YE, Ginsburg C, Riou B. Unprecedented heat-related deaths during the 2003 heat wave in Paris: Consequences on emergency departments. *Crit Care*. 2004;8:1–2.

51. Gardner JW, Kark JA. Clinical diagnosis, management, and surveillance of exertional heat illness. In: Pandolf KB, Burr RE, Wenger CB, Pozos RS, eds. *Medical Aspects of Harsh Environments,* Volume 1. In: Zajtchuk R, Bellamy RF, eds. *Textbook of Military Medicine.* Washington, DC: Department of the Army, Office of The Surgeon General, Borden Institute; 2001: Chap 7. Available at: http://www.bordeninstitute.army.mil. Accessed December 26, 2005.

52. Shibasaki M, Sakai M, Oda M, Crandall CG. Muscle mechanoreceptor modulation of sweat rate during recovery from moderate exercise. *J Appl Physiol*. 2004;96:2115–2119.

53. Knochel JP. Heat stroke and related heat stress disorders. *Dis Mon*. 1989;35:301–377.

54. Kellum JAD, Janine M, Kelso L. The immune system: Relation to sepsis and multiple organ failure. *Am Acad Clin Nurs*. 1996;7:339–350.

55. Mustafa S, Thulesius O, Ismael HN. Hyperthermia-induced vasoconstriction of the carotid artery, a possible causative factor of heatstroke. *J Appl Physiol*. 2004;96:1875–1878.

56. Nielsen B, Nybo L. Cerebral changes during exercise in the heat. *Sports Med*. 2003;33:1–11.

57. Allison RC, Bedsole DL. The other medical causes of rhabdomyolysis. *Am J Med Sci*. 2003;326:79–88.

58. Coco TJ, Klasner AE. Drug-induced rhabdomyolysis. *Curr Opin Pediatr*. 2004;16:206–210.

59. Ellenhorn M, ed. *Ellenhorn's Medical Toxicology: Diagnosis and Treatment of Human Poisoning*. 2nd ed. Baltimore, Md: Williams & Wilkins; 1997.

60. Malinoski DJ, Slater MS, Mullins RJ. Crush injury and rhabdomyolysis. *Crit Care Clin*. 2004;20:171–192.

61. Kark JA, Larkin TJ, Hetzel DP, Jarmulowitz MA, Lindgren KM, Gardner JW. Exertional heat illness contributing to sudden cardiac death. *Circulation*. 1997;96:476.

62. Arking DE, Chugh SS, Chakravarti A, Spooner PM. Genomics in sudden cardiac death. *Circ Res*. 2004;94:712–723.

63. Wilde AA, Antzelevitch C, Borggrefe M, et al. Proposed diagnostic criteria for the Brugada syndrome. *Eur Heart J*. 2002;23:1648–1654.

64. Giercksky T, Boberg KM, Farstad IN, Halvorsen S, Schrumpf E. Severe liver failure in exertional heat stroke. *Scand J Gastroenterol*. 1999;34:824–827.

65. Szabo G, Romics L Jr, Frendl G. Liver in sepsis and systemic inflammatory response syndrome. *Clin Liver Dis*. 2002;6:1045–1066.

66. Hakre S, Gardner JW, Kark JA, Wenger CB. Predictors of hospitalization in male Marine Corps recruits with exertional heat illness. *Mil Med*. 2004;169:169–175.

67. Sass DA, Shakil AO. Fulminant hepatic failure. *Gastroenterol Clin North Am*. 2003;32:1195–1211.

68. Shakil AO, Kramer D, Mazariegos GV, Fung JJ, Rakela J. Acute liver failure: Clinical features, outcome analysis, and applicability of prognostic criteria. *Liver Transpl.* 2000;6:163–169.

69. Wagner M, Kaufmann P, Fickert P, Trauner M, Lackner C, Stauber RE. Successful conservative management of acute hepatic failure following exertional heatstroke. *Eur J Gastroenterol Hepatol.* 2003;15:1135–1139.

70. Berger J, Hart J, Millis M, Baker AL. Fulminant hepatic failure from heat stroke requiring liver transplantation. *J Clin Gastroenterol.* 2000;30:429–431.

71. Lin YF, Wang JY, Chou TC, Lin SH. Vasoactive mediators and renal haemodynamics in exertional heat stroke complicated by acute renal failure. *Q J Med*. 2003;96:193–201.

72. Yegenaga I, Hoste E, Van Biesen W, et al. Clinical characteristics of patients developing ARF due to sepsis/systemic inflammatory response syndrome: Results of a prospective study. *Am J Kidney Dis*. 2004;43:817–824.

73. Bone RC, Balk RA, Cerra FB, et al. Definitions for sepsis and organ failure and guidelines for the use of innovative therapies in sepsis. The ACCP/SCCM Consensus Conference Committee. American College of Chest Physicians/Society of Critical Care Medicine. *Chest*. 1992;101:1644–1655.

74. Colligan N, Giannoudis PV, Kourgeraki O, Perry SL, Guillou PJ, Bellamy MC. Interleukin 13 and inflammatory markers in human sepsis. *Br J Surg*. 2004;91:762–768.

75. Camus G, Deby-Dupont G, Duchateau J, Deby C, Pincemail J, Lamy M. Are similar inflammatory factors involved in strenuous exercise and sepsis? *Intensive Care Med.* 1994;20:602–610.

76. Bugajski AJ, Thor P, Glod R, Gadek-Michalska A, Bugajski J. Influence of cyclooxygenase inhibitors on the central histaminergic stimulations of hypothalamic-pituitary-adrenal axis. *J Physiol Pharmacol*. 2003;54:643–652.

77. Marik PF, Zaloga GP. Adrenal insufficiency during septic shock. *Crit Care Med.* 2003;31:141-145.

78. Volk HD, Reinke P, Krausch D, et al. Monocyte deactivation: Rationale for a new therapeutic strategy in sepsis. *Intensive Care Med.* 1996;22(suppl 4):S474-S481.

79. Yanagimoto, S, Kuwahara T, Zhang Y, Koga S, Inoue Y, Kondo N. Intensity-dependent thermoregulatory responses at the onset of dynamic exercise in mildly heated humans. *Am J Physiol Regul Integr Comp Physiol*. 2003;285:R200–R207.

80. Vallet B. Bench-to-bedside review: Endothelial cell dysfunction in severe sepsis: A role in organ dysfunction? *Crit Care.* 2003;7:130–138.

81. Backer HD, Shopes E, Collins SL, Barkan H. Exertional heat illness and hyponatremia in hikers. *Am J Emerg Med*. 1999;17:532–539.

82. Gaffin SL, Gardner JW, Flinn SD. Cooling methods for heatstroke victims. *Ann Intern Med*. 2000;132:678.

83. Whitman W. *Prose Works*. Philadelphia, Pa: David McKay; 1892. Available at: http://www.bartleby.com. Accessed December 26, 2005.

84. US Army Center for Health Promotion and Preventive Medicine. *Heat Stress Control and Heat Casualty Management*. Washington, DC: Headquarters, DA, DN, and DAF; 7 March 2003. TB Med507/AFPAM 48-152(I). Technical Bulletin. Available at: http://chppm-www.apgea.army.mil/heat/. Accessed December 26, 2005.