Severe nonexertional hyperthermia (classic heat stroke) in adults

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INTRODUCTION

Hyperthermia is defined as elevation of core body temperature above the normal diurnal range of 36 to 37.5°C due to failure of thermoregulation. Hyperthermia is not synonymous with the more common sign of fever, which is induced by cytokine activation during inflammation and regulated at the level of the hypothalamus. A temperature above 40.5°C (or 105°F) is generally considered to be consistent with severe hyperthermia.

The evaluation of severe hyperthermia in adults and the management of nonexertional heat stroke are reviewed here. Other causes of hyperthermia are discussed separately:

- Exertional heat illness (including exertional heat stroke) (see "Exertional heat illness in adolescents and adults: Epidemiology, thermoregulation, risk factors, and diagnosis" and "Exertional heat illness in adolescents and adults: Management and prevention")
- Fever in adults, malignant hyperthermia, and neuroleptic malignant syndrome (NMS) (see "Pathophysiology and treatment of fever in adults" and "Malignant hyperthermia: Diagnosis and management of acute crisis" and "Neuroleptic malignant syndrome")
- Hyperthermia in children (see "Heat stroke in children" and "Fever in infants and children: Pathophysiology and management")

PATHOPHYSIOLOGY

Body temperature is maintained within a narrow range by balancing heat load with heat dissipation [1-3]. The body's heat load results from both metabolic processes and absorption of heat from the environment. As core temperature rises, the preoptic nucleus of the anterior hypothalamus stimulates efferent fibers of the autonomic nervous system to produce sweating and cutaneous vasodilation.

Evaporation is the principal mechanism of heat loss in a hot environment, but this becomes ineffective above a relative humidity of 75 percent [4]. The other major methods of heat dissipation – radiation (emission of infrared electromagnetic energy), conduction (direct transfer of heat to an adjacent, cooler object), and convection (direct transfer of heat to convective air currents) – cannot efficiently transfer heat when environmental temperature exceeds skin temperature. The normal regulation of body temperature is discussed separately. (See "Exertional heat illness in adolescents and adults: Epidemiology, thermoregulation, risk factors, and diagnosis", section on 'Thermoregulation in the heat'.)

Temperature elevation is accompanied by an increase in oxygen consumption and metabolic rate, resulting in hyperpnea and tachycardia. A cytokine-mediated systemic inflammatory response develops, and production of heat-shock proteins is increased. Blood is shunted from the splanchnic circulation to the skin and muscles, resulting in gastrointestinal ischemia and increased permeability of the intestinal mucosa [5]. Hepatocytes, vascular endothelium, and neural tissue are most sensitive to increased core temperatures, but all organs may ultimately be involved. In severe cases, patients develop multi-organ-system failure and disseminated intravascular coagulation (DIC) [2,6-8]. Above 42°C (108°F), oxidative phosphorylation becomes uncoupled, and a variety of enzymes cease to function.

Several of the physiologic mechanisms for coping with an increased environmental heat load are impaired in the very young and very old. These include reduced ability to deliver heat to the skin, reduced epidermal area available for heat transfer, and impaired vasodilation of the skin. These and other related problems are described in greater detail separately. (See "Heat stroke in children", section on 'Pathophysiology' and "Normal aging".)

DEFINITIONS

Heat stroke is defined as an elevated core body temperature, usually in excess of 40.5°C (105°F), with associated central nervous system dysfunction in the setting of a large environmental heat load that cannot be dissipated [2,9,10]. It is a potentially fatal condition that requires rapid identification and treatment [11].

There are two types of heat stroke:

- **Nonexertional (classic) heat stroke** – Nonexertional heat stroke affects individuals with a physiologic or anatomic predisposition or underlying chronic medical conditions that impair thermoregulation, prevent removal from a hot environment, or interfere with access to hydration or attempts at cooling [12]. Such predispositions and conditions include cardiovascular disease, neurologic or psychiatric disorders, obesity, anhidrosis, physical disability, extremes of age, and the use of recreational drugs (eg, alcohol or cocaine) and certain prescription drugs (eg, beta-blockers, diuretics, or anticholinergic agents) [2,13-15]. While adults over 70 years of age are most often affected, small children left in vehicles during warm weather die from heat stroke every year [16]. (See "Heat stroke in children".)

- **Exertional heat stroke** – Exertional heat stroke generally occurs in young, otherwise healthy individuals who engage in heavy exercise during periods of high ambient temperature and humidity. Typical patients are athletes and military recruits in basic training. In vitro muscle fiber testing reveals evidence of susceptibility to malignant hyperthermia in some patients who present in this fashion [17,18]. Exertional heat stroke is discussed in detail separately. (See "Exertional heat illness in adolescents and adults: Epidemiology, thermoregulation, risk factors, and diagnosis" and "Exertional heat illness in adolescents and adults: Management and prevention".)

RISK FACTORS

Factors associated with increased mortality — Patients who present to the hospital with heat stroke have high mortality, with rates ranging from 21 to 63 percent [3,19-21]. Mortality correlates with the degree of temperature elevation, time to initiation of cooling measures, and the number of organ systems affected [22]. According to one prospective cohort study, the risk of death increases substantially in patients who present with anuria (hazard ratio [HR] 5.24; 95% CI 2.29-12.03), coma (HR 2.95; 95% CI 1.26-6.91), or cardiovascular failure (HR 2.43; 95% CI 1.14-5.17) [20]. The development of disseminated intravascular coagulation (DIC) is associated with increased mortality [23].

Factors associated with increased risk — Important risk factors for the development of nonexertional (classic) heat stroke include extremes of age, pregnancy, obesity, poor physical condition, lack of acclimatization, lack of air-conditioning, and social isolation [3,20,24-26]. Dehydration resulting from inadequate water intake to replace fluids lost by sweating is an important factor. Other risk factors include diabetes, cardiovascular disease, heavy alcohol use, and a number of medications and illicit drugs. These include diuretics, medications with anticholinergic properties, sympathomimetics, salicylates, and the antiepileptic topiramate [27-29]. The following table lists some drugs that can increase core body temperature (table 1).

CLINICAL PRESENTATION

Patients with nonexertional (classic) heat stroke present with an elevated core body temperature, usually in excess of 40.5°C (105°F), that is not due to exertion and is associated with central nervous system dysfunction in the setting of a large environmental heat load that cannot be dissipated [2,9].

In addition to an elevated core body temperature, common vital sign abnormalities in nonexertional heat stroke include sinus tachycardia, tachypnea, a widened pulse pressure, and hypotension [10,30]. The temperature reading of some patients with heat stroke may not exceed 40°C, particularly if cooling measures were initiated prior to the patient's arrival at the hospital. In addition, some standard thermometers have a maximum reading below the temperatures sometimes reached by patients suffering from heat stroke and thus give inaccurate and misleading information. A thermometer (rectal or esophageal) that is accurate at high temperatures must be used when assessing patients with possible heat stroke.

If they can respond coherently, patients with heat stroke may complain of weakness, lethargy, nausea, or dizziness. The presentation of older adults with heat stroke may be subtle and nonspecific early in the course of the disease.

Other physical findings may include flushing (cutaneous vasodilation), tachypnea, crackles due to noncardiogenic pulmonary edema, and manifestations of coagulopathy (with potential bleeding complications ranging in severity from petechiae and ecchymoses to intracranial hemorrhage). Signs of neurologic dysfunction may include altered mentation, slurred speech, irritability, inappropriate behavior, agitation, ataxia and other signs of poor coordination, delirium, seizures, and coma [2,31]. The skin may be moist or dry depending upon underlying medical conditions, the speed with which the heat stroke developed, and hydration status [30]. Not all victims of heat stroke are volume depleted [32].

Frequently encountered complications include acute respiratory distress syndrome (ARDS), disseminated intravascular coagulation (DIC), acute kidney injury (ie, acute renal failure), hepatic injury, hypoglycemia, rhabdomyolysis, and seizures [2]. (See 'Complications and sequelae' below.)

DIAGNOSIS

The diagnosis of nonexertional (classic) heat stroke is made clinically based upon an elevated core body temperature (generally >40.5°C [105°F]), central nervous system dysfunction (eg, altered mental status), and exposure to severe environmental heat [2]. Patients with classic heat stroke generally have increased susceptibility to the heat due to age or underlying medical conditions, manifest characteristic examination findings, and lack an alternative explanation for their hyperthermia (eg, infection). In addition to an elevated core body temperature, common examination findings in nonexertional (classic) heat stroke include vital sign abnormalities (eg, tachycardia, tachypnea, hypotension), flushing, pulmonary crackles, oliguria, and neurologic abnormalities.

DIAGNOSTIC EVALUATION

Core temperature — A rectal temperature should be obtained in all patients suspected of heat stroke. Some standard thermometers have a maximum reading below the temperatures sometimes reached by patients suffering from heat stroke and thus may give inaccurate and misleading information. A thermometer (rectal or esophageal) that is accurate at high temperatures must be used to assess and monitor heat stroke patients.

Diagnostic testing — A chest radiograph should be obtained and may demonstrate pulmonary edema. The electrocardiogram (ECG) may reveal dysrhythmias, conduction disturbances, nonspecific ST-T wave changes, or heat-related myocardial ischemia or infarction [33-35]. Laboratory studies may reveal coagulopathy, acute kidney injury (acute renal failure), acute hepatic necrosis, elevated serum troponin, and a leukocytosis as high as 30,000 to 40,000/mm^3 [1,2].

Laboratory studies to obtain in the patient with nonexertional heat stroke include:

- Complete blood count, basic serum electrolyte concentrations, blood urea nitrogen (BUN) and creatinine concentrations, and hepatic transaminase concentrations. Transaminase concentrations are rarely normal in patients with heat stroke; however, in patients with severe liver injury, marked elevations may not appear for 24 to 48 hours [22,36-38]. (See "Acute liver failure in adults: Management and prognosis", section on 'Laboratory testing'.)

- Prothrombin time (PT), international normalized ratio (INR), and partial thromboplastin time (PTT) because of the risk of heat-induced liver damage and disseminated intravascular coagulation (DIC) [39]. (See "Evaluation and management of disseminated intravascular coagulation (DIC) in adults".)

- Arterial or venous blood gas – Metabolic acidosis and respiratory alkalosis are the most common abnormalities [40]. The serum lactate concentration is frequently elevated. (See "Simple and mixed acid-base disorders".)

- Studies to detect rhabdomyolysis (eg, serum creatine kinase, urine myoglobin) and its complications (eg, hypocalcemia, hyperphosphatemia, myoglobinuria, and BUN and creatinine) [41]. Myoglobinuria should be suspected in any patient with brown urine supernatant that is heme-positive and clear plasma. Urinalysis may reveal other evidence of kidney injury, including protein, blood, tubular casts, and increased specific gravity [42]. (See "Rhabdomyolysis: Clinical manifestations and diagnosis" and "Clinical features and diagnosis of heme pigment-induced acute kidney injury".)

- Toxicologic screening may be indicated if a medication effect is suspected. Drugs that may contribute to hyperthermia and for which tests are often available include ethanol, amphetamines, cocaine, salicylates, hallucinogens, and lithium. (See "General approach to drug poisoning in adults" and "Initial management of the critically ill adult with an unknown overdose".)

- A head computed tomography (CT) scan and analysis of the cerebrospinal fluid should be performed as indicated if central nervous system causes of altered mental status are suspected [30].

DIFFERENTIAL DIAGNOSIS

The differential diagnosis of severe hyperthermia is extensive and includes infectious, endocrine, central nervous system, toxic, and oncologic etiologies (table 2).

Nonexertional (classic) heat stroke can often be distinguished from other conditions based solely upon the history and physical examination, particularly in at-risk patients during a heat wave. However, the clinical picture can be unclear. As examples, an older adult woman found unconscious in a sealed house in the middle of summer who has a core temperature of 41.2°C (106.2°F) presents many more diagnostic possibilities than a college football player who collapses during summer practice and has the same temperature. The woman may be suffering from sepsis, cerebral hemorrhage, anticholinergic toxicity, withdrawal from a central nervous system depressant, or a host of other conditions. Conversely, her elevated temperature may be due solely to heat exposure.

No single diagnostic test definitively confirms or excludes heat stroke. Furthermore, laboratory study abnormalities may overlap in patients with heat stroke and with hyperthermia due to other conditions. As an example, patients with heat stroke frequently meet criteria for the systemic inflammatory response syndrome (SIRS) [43]. It may be impossible early in the patient's course to distinguish the two conditions. In such cases when the etiology of hyperthermia is unclear but heat stroke remains a possibility, it is prudent to initiate cooling measures while diagnoses other than heat stroke are pursued.

Rapid improvement with active cooling suggests that heat stroke is the primary diagnosis. However, improvement may not occur or may occur gradually, particularly in older debilitated patients, depending upon the degree and duration of hyperthermia and other factors. As an example, patients with compromised cardiovascular function due to underlying disease (eg, heart failure) or medications (eg, beta or calcium channel blocker) have limited capacity to respond to increased environmental heat and humidity [44]. In patients whose mental status remains depressed despite effective cooling measures, clinicians should investigate alternative causes for hyperthermia, including conditions affecting the central nervous system (eg, meningitis, cerebral hemorrhage, hypothalamic stroke). Brain imaging and analysis of cerebrospinal fluid may be necessary.

The most important causes of severe hyperthermia (greater than 40.5°C [105°F]) due to a failure of thermoregulation are heat stroke, neuroleptic malignant syndrome (NMS), and malignant hyperthermia. The context in which symptoms develop usually suggests the etiology (eg, exertional heat stroke following exercise in high ambient temperature and humidity, NMS among patients treated with antipsychotic medications, or malignant hyperthermia after anesthetic agents). Each of these conditions may be associated with severe systemic complications and death.

Malignant hyperthermia is a rare autosomal dominant disorder that manifests most often following treatment with anesthetic agents, most commonly succinylcholine and halothane. The onset of malignant hyperthermia is usually within one hour of the administration of general anesthesia but rarely may be delayed up to 10 hours after induction. Early clinical findings include muscle rigidity (especially masseter stiffness), sinus tachycardia, hypercarbia, and skin cyanosis with mottling. Marked hyperthermia (up to 45°C [113°F]) occurs minutes to hours later. A syndrome similar to malignant hyperthermia but unrelated to anesthesia has been described and sometimes referred to as "awake malignant hyperthermia." Patients exhibit unexplained, stress-induced (possibly related to hot environment or exercise) temperature elevation, muscle cramping or rigidity, and other characteristics associated with malignant hyperthermia. (See "Malignant hyperthermia: Diagnosis and management of acute crisis" and "Susceptibility to malignant hyperthermia: Evaluation and management", section on 'Non-anesthesia-related MH-like episodes'.)

NMS is an idiosyncratic reaction most frequently associated with first- and second-generation antipsychotic agents. The following table includes a list of drugs associated with NMS (table 3). In addition to hyperthermia, NMS is also characterized by "lead pipe" muscle rigidity, altered mental status, choreoathetosis, tremors, and evidence of autonomic dysfunction such as diaphoresis, labile blood pressure, and dysrhythmias. (See "Neuroleptic malignant syndrome".)

MANAGEMENT

Recommendations for the treatment of nonexertional (classic) heat stroke are based primarily on case series and small observational studies. There is little high-quality evidence to guide care. The management of nonexertional (classic) heat stroke requires early diagnosis, rapid cooling, correction of electrolyte abnormalities, and supportive care [2,10,11]. The management of exertional heat stroke is discussed separately. (See "Exertional heat illness in adolescents and adults: Management and prevention".)

Management of the airway and hypotension — Tracheal intubation and mechanical ventilation are needed for patients unable to protect their airway or with deteriorating respiratory function. For patients with persistent seizures prior to intubation, monitoring with an electroencephalogram is prudent until the core temperature is lowered [45]. (See "Rapid sequence intubation in adults for emergency medicine and critical care" and "Mechanical ventilation of adults in the emergency department".)

Point-of-care ultrasound may be useful for assessing volume status and determining the need for fluid resuscitation [46] (see "Novel tools for hemodynamic monitoring in critically ill patients with shock", section on 'Point-of-care ultrasonography'). If ultrasound is unavailable, adequate fluid resuscitation can be guided by heart rate, blood pressure, and urine output; central venous pressure measurements may be unreliable due to cardiovascular dysfunction [47].

Alpha-adrenergic agonists should be avoided, as the resultant vasoconstriction decreases heat dissipation. Instead, hypotension or volume depletion is treated with discrete intravenous (IV) boluses of isotonic crystalloid (eg, isotonic saline in boluses of 250 to 500 mL).

Little evidence is available to guide the management, including selection of vasoactive drugs, of patients who remain hypotensive despite fluid resuscitation and cooling measures, particularly patients with underlying cardiac disease. Because of pathophysiologic similarities between heat stroke and sepsis, it has been suggested that vasoactive agents used to treat septic shock may be appropriate for heat stroke patients. Norepinephrine is a reasonable first-line agent, followed by epinephrine, and dobutamine may be appropriate in select patients requiring inotropic support. (See "Evaluation and management of suspected sepsis and septic shock in adults", section on 'Vasopressors'.)

Cooling measures and temperature monitoring — Rapid cooling is a key determinant of a favorable outcome. Evaporative and convective cooling is the method used most often to treat nonexertional (classic) heat stroke because it is effective, noninvasive, and easily performed; and does not interfere with other aspects of patient care. When used to treat older adult patients with nonexertional heat stroke, evaporative and convective cooling is associated with decreased morbidity and mortality [6,48-50].

To perform evaporative and convective cooling, the naked patient is sprayed with a mist of lukewarm water while fans are used to blow air over the moist skin. Special beds called body cooling units have been made for this purpose [6].

Agitation from an altered mental status or shivering induced by evaporative and convective cooling or other treatments may generate heat and can be suppressed with short-acting IV benzodiazepines, such as lorazepam (1 to 2 mg IV). Benzodiazepines may also improve core body cooling [51]. Other options to control shivering include propofol, opioids such as fentanyl, and, for refractory cases, neuromuscular blocking agents (eg, rocuronium). (See "Initial assessment and management of the adult post-cardiac arrest patient", section on 'Sedation and suppression of shivering'.)

Continuous core temperature monitoring with a rectal or esophageal probe is mandatory. Little published evidence is available to inform cooling goals, but we think that evaporative and convective cooling measures should be discontinued once a core body temperature of 36°C is achieved.

It is recommended that cooling measures be stopped once a temperature of 38 to 39°C (100.4 to 102.2°F) is achieved in order to reduce the risk of iatrogenic hypothermia caused by an afterdrop in temperature [30]. According to a case series of three patients, a period of therapeutic hypothermia below 36°C following initial cooling may improve neurologic outcome by reducing direct heat-related toxicity, neuronal damage, and the heat-related inflammatory response [52]. However, unless further evidence to support this approach becomes available, it is reasonable to continue using 38 to 39°C as an appropriate goal for cooling.

Other effective cooling methods are less commonly used in patients with nonexertional heat stroke. Immersing the patient in ice water (cold water immersion) is perhaps the most rapid, noninvasive method of cooling [6], but it complicates monitoring and IV access and may be harmful to older adult patients [2]. An alternative method that allows greater access to the patient is water ice therapy (WIT), in which the patient is placed supine on a porous stretcher positioned on top of a tub of ice water. Medical personnel continuously pour ice water from the bath onto the patient and massage major muscle groups with ice packs to increase skin vasodilation [53]. Applying ice packs to the axillae, neck, and groin (areas adjacent to major blood vessels) is effective as an adjunct cooling technique, but it may be poorly tolerated by the awake patient.

A small randomized trial, in healthy subjects with exercise-induced hyperthermia, reported that applying cold compresses to the glabrous (smooth, hairless) skin surfaces of the cheeks, palms, and soles led to more rapid cooling than applying them to the axillae, neck, and groin [54]. This approach warrants further study in nonexertional heat stroke patients with comorbidities that might impair peripheral vasodilatation.

Cold pleural or peritoneal lavage results in rapid cooling. However, both are invasive, and peritoneal lavage is contraindicated in pregnant patients and those with previous abdominal surgery. Cooled oxygen, cooling blankets, and cold (ie, room temperature, or approximately 22°C [71.6°F]) IV fluids may be helpful adjuncts. Cold gastric lavage may cause water intoxication [55].

A case report describes the use of an intranasal cooling device to treat an 80-year-old male suffering from nonexertional heat stroke with a core temperature of 42°C [56]. Other reports describe intranasal cooling being used to induce therapeutic hypothermia in critically ill, intubated, postcardiac arrest patients [57]. Given the practical challenges of cooling critical patients using the methods described above, nasal cooling may be a viable alternative if a device is available.

Alcohol sponge baths should be avoided because large amounts of the drug may be absorbed through dilated cutaneous vessels and produce toxicity [1].

Pharmacologic therapy — Pharmacologic therapy is not required in heat stroke. There is no role for antipyretic agents such as acetaminophen or aspirin in the management of heat stroke since the underlying mechanism does not involve a change in the hypothalamic set-point, and these medications may exacerbate complications such as hepatic injury or disseminated intravascular coagulation (DIC) [30]. Salicylates can contribute to hyperthermia by uncoupling oxidative phosphorylation. Dantrolene is ineffective in patients with severe temperature elevation **not** caused by malignant hyperthermia [58,59]. In cases where the etiology of the patient's hyperthermia is unclear initially and infection remains a possibility, empiric administration of an initial dose of antibiotics, following collection of appropriate cultures, is prudent while cooling measures are implemented.

COMPLICATIONS AND SEQUELAE

Severe nonexertional hyperthermia may lead to a wide range of complications. These often resolve as cooling measures take effect, but this depends upon the degree and duration of hyperthermia. Potential complications are described below.

The long-term sequelae of nonexertional (classic) heat stroke are not well studied but likely depend upon the duration of exposure, the extent of injury, and the organ system-specific, short-term complications sustained. Much of what is known comes from case reports involving either exertional or nonexertional heat stroke. A study of 150 patients with heat stroke or other heat-related illness who were followed for 14 years found that affected patients were at greater risk for myocardial infarction, ischemic stroke, or chronic kidney disease compared with a control group [60].

Regardless of organ systems involved, survivors of heat stroke can experience long-term functional and neurologic impairment. In August 2003, Europe endured an extreme heat wave that caused 14,800 heat-related deaths in France alone. A prospective study of 83 patients admitted to one hospital looked at short- and long-term mortality and functional outcome. The two-year mortality was 71 percent, with most patients surviving two years having significant functional impairment [20]. Similar long-term impairment was noted in survivors of the July 1995 Chicago (United States) heat wave, which caused 600 excess deaths [19].

- **Respiratory dysfunction** − Patients with nonexertional heat stroke often develop pulmonary complications, which can include aspiration, bronchospasm, noncardiogenic pulmonary edema, acute respiratory distress syndrome, pneumonitis, pulmonary infarction, and pulmonary hemorrhage. Tracheal intubation and mechanical ventilation are often necessary to protect the airway and to address increased metabolic demands (ie, provide supplemental oxygen and increased minute ventilation). In a review of 28 patients admitted with heat stroke, 24 (86 percent) developed respiratory failure with most requiring mechanical ventilation [37]. (See "Rapid sequence intubation in adults for emergency medicine and critical care" and "Acute respiratory distress syndrome: Fluid management, pharmacotherapy, and supportive care in adults" and "Ventilator management strategies for adults with acute respiratory distress syndrome".)

- **Arrhythmia and cardiac dysfunction** – Potential cardiac complications include acute decompensated heart failure and myocardial injury associated with reversible cardiac biomarker increase and ST-segment changes on electrocardiogram (ECG). The biomarker and ECG changes are believed to be caused by an increase in catecholamine levels due to heat stroke, causing a stress-induced cardiomyopathy [61,62]. Other ECG abnormalities that have been reported in association with heat stroke include sinus tachycardia and other tachyarrhythmias, conduction abnormalities, prolonged QT interval, transient Brugada pattern, and nonspecific ST-T changes [34,63]. Rapid cooling is essential; cardiac dysfunction and tachyarrhythmias generally resolve with cooling. Antiarrhythmics are seldom necessary, and electrical cardioversion should be avoided until cooling is achieved unless necessary to treat ventricular fibrillation or pulseless ventricular tachycardia. (See "Clinical manifestations and diagnosis of stress (takotsubo) cardiomyopathy" and "Management and prognosis of stress (takotsubo) cardiomyopathy" and "Advanced cardiac life support (ACLS) in adults".)

- **Hypotension** − Hypotension associated with heat stroke results from peripheral vasodilation, cardiac dysfunction, and volume depletion. Treatment consists primarily of discrete intravenous (IV) boluses of isotonic crystalloid (eg, isotonic saline 250 to 500 mL). Given the risk of pulmonary edema, excessive fluid administration should be avoided. Alpha-adrenergic agonists cause vasoconstriction, which impairs cooling, and these should be avoided if possible.

- **Seizures** − Seizures are common in patients with heat stroke. Initial treatment consists of short-acting benzodiazepines in incremental doses while cooling measures are initiated. Lorazepam, 0.1 mg/kg IV every five minutes until seizures stop, is a first-line agent. Midazolam, 10 mg intramuscularly (IM), is an effective alternative when IV access cannot easily be obtained. Rapid cooling is essential to treatment. (See "Convulsive status epilepticus in adults: Management", section on 'First therapy: Benzodiazepines'.)

- **Cerebral edema and neurologic injury** − In addition to seizures, cerebral edema is common following heat stroke. A variety of cerebrovascular injuries, neuropathies, and cerebellar ataxia may occur [64-67]. Guillain-Barre syndrome and Parkinsonism have been reported [66,68]. Pathologic changes may include petechiae in the ventricle walls and damage to cerebellar Purkinje cells.

- **Rhabdomyolysis** − The combination of muscle injury, volume depletion, and acute kidney injury can lead to rhabdomyolysis in patients with heat stroke. Standard therapies are used for treatment, and these are discussed separately. (See "Clinical features and diagnosis of heme pigment-induced acute kidney injury" and "Prevention and treatment of heme pigment-induced acute kidney injury (including rhabdomyolysis)".)

- **Acute kidney injury** − Heat stroke can cause acute kidney injury. Kidney function studies and serum electrolyte concentrations should be followed closely over the first few days of illness; kidney replacement therapy (eg, hemodialysis) may be needed [22]. (See "Overview of the management of acute kidney injury (AKI) in adults".)

- **Hepatic injury** – Hepatic injury due to heat stroke is generally self-limited but in some cases may progress to acute liver failure, with a subset of patients requiring liver transplantation [69]. (See "Acute liver failure in adults: Etiology, clinical manifestations, and diagnosis" and "Acute liver failure in adults: Management and prognosis".)

- **Disseminated intravascular coagulation (DIC)** − DIC can develop during the first three days of illness, and coagulation studies should be monitored during this period. Replacement of clotting factors with fresh frozen plasma and platelets may be necessary. (See "Evaluation and management of disseminated intravascular coagulation (DIC) in adults".)

SOCIETY GUIDELINE LINKS

Links to society and government-sponsored guidelines from selected countries and regions around the world are provided separately. (See "Society guideline links: Management of environmental emergencies".)

INFORMATION FOR PATIENTS

UpToDate offers two types of patient education materials, "The Basics" and "Beyond the Basics." The Basics patient education pieces are written in plain language, at the 5th to 6th grade reading level, and they answer the four or five key questions a patient might have about a given condition. These articles are best for patients who want a general overview and who prefer short, easy-to-read materials. Beyond the Basics patient education pieces are longer, more sophisticated, and more detailed. These articles are written at the 10th to 12th grade reading level and are best for patients who want in-depth information and are comfortable with some medical jargon.

Here are the patient education articles that are relevant to this topic. We encourage you to print or e-mail these topics to your patients. (You can also locate patient education articles on a variety of subjects by searching on "patient info" and the keyword(s) of interest.)

- Basics topic (see "Patient education: Heat stroke (The Basics)")

SUMMARY AND RECOMMENDATIONS

- **Body temperature and pathophysiology** – Body temperature is maintained within a narrow range by balancing heat load with heat dissipation. Evaporation is the principal mechanism of heat loss in a hot environment but becomes ineffective above a relative humidity of 75 percent. The other major methods of heat dissipation, including conduction and convection, cannot efficiently transfer heat when environmental temperature exceeds skin temperature. (See 'Pathophysiology' above.)

- **Differential diagnosis** – The differential diagnosis of hyperthermia is extensive and includes infectious, endocrine, central nervous system, and toxic etiologies (table 2). The most important causes of severe hyperthermia (greater than 40.5°C [or 105°F]) caused by a failure of thermoregulation are heat stroke, neuroleptic malignant syndrome (NMS) (table 3), and malignant hyperthermia. (See "Neuroleptic malignant syndrome" and "Malignant hyperthermia: Diagnosis and management of acute crisis".)

- **Mortality risk** – Severe nonexertional (classic) heat stroke carries a high mortality rate.

Mortality correlates with the degree of temperature elevation, time to initiation of cooling measures, and the number of organ systems affected. Patients with nonexertional heat stroke generally have increased susceptibility to the heat due to age or underlying medical conditions. (See 'Risk factors' above.)

- **Diagnosis and diagnostic testing** – Diagnosis is made clinically based upon an elevated core body temperature (generally greater than 40.5°C [105°F]), central nervous system dysfunction (eg, altered mental status), exposure to severe environmental heat, and the absence of another explanation for hyperthermia. Diagnostic studies are generally nonspecific but may reflect cardiovascular, kidney, or hepatic dysfunction, or coagulopathy. Studies to be obtained are described in the text. (See 'Definitions' above and 'Diagnosis' above and 'Diagnostic evaluation' above.)

- **Management** – Management consists of ensuring adequate airway protection, breathing, and circulation; rapid cooling; and treatment of complications. Tracheal intubation and mechanical ventilation are often necessary. Hypotension or volume depletion is treated with discrete intravenous (IV) boluses of isotonic crystalloid; alpha-adrenergic agonists should be avoided if possible. (See 'Management' above.)

  We suggest that rapid cooling of patients with nonexertional heat stroke be performed using evaporative and convective techniques, rather than other noninvasive (eg, cold water immersion) or invasive (eg, peritoneal lavage) techniques (**Grade 2C**). Evaporative and convective cooling techniques are safe and effective and do not interfere with patient access or monitoring, or with other treatments. Cold water immersion may be harmful to older adult patients; there is no role for antipyretic agents. Continuous core temperature monitoring with a rectal or esophageal probe is mandatory in all patients being treated for heat stroke. We discontinue cooling measures when a core temperature of 36°C is achieved. (See 'Cooling measures and temperature monitoring' above.)

  The management of exertional heat stroke is discussed separately. (See "Exertional heat illness in adolescents and adults: Management and prevention".)

- **Complications** – Complications of nonexertional heat stroke may include respiratory and cardiac dysfunction, hypotension, seizures, cerebral edema, neurologic injury, rhabdomyolysis, acute kidney or hepatic injury, and disseminated intravascular coagulation (DIC). (See 'Complications and sequelae' above.)

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Topic 176 Version 33.0

Drug- and toxin-induced temperature abnormalities

Hyperthermia
Increased heat production
Muscular hyperactivity/rigidity
Sympathomimetics
Cocaine
Amphetamines
Phenylpropanolamine
Ephedrine
Cathinones
Anticholinergics
Drug withdrawal states
Lithium
Central hallucinogens
Phencyclidine
Lysergic acid diethylamide (LSD)
Designer amphetamines (MDMA, MDEA)
Synthetic cannabinoids
Drugs causing recurrent seizures
Isoniazid
Theophylline
Phenethylamines
Strychnine
Neuroleptic malignant syndrome
Serotonin syndrome
MAO inhibitors
Malignant hyperthermia
Impaired heat dissipation

Hypothermia
Opioids
Sedative-hypnotics
Benzodiazepines
Barbiturates
Alcohols
Sympatholytics
Beta blockers
Clonidine
Alpha-adrenergic antagonists
Hypoglycemic agents
Antipsychotics
General anesthetic agents
Carbon monoxide
Drugs which cause flaccid coma

Impaired sweating
Anticholinergic agents
Antihistamines
Phenothiazines
Tricyclic antidepressants
Increased metabolic rate
Uncoupled oxidative phosphorylation
Salicylates
Dinitrophenol, pentachlorophenol
Thyroid hormone

Graphic 55439 Version 9.0

Differential diagnosis of hyperthermia*

Infection	Drug or toxin related	Neurologic	Environmental	Endocrine
Sepsis	Malignant hyperthermia	Hypothalamic stroke	High temperature and humidity	Thyroid storr
Meningitis	Neuroleptic malignant syndrome	Status epilepticus		Pheochromo
Encephalitis	Withdrawal syndromes (eg, alcohol, sedative hypnotic)	Cerebral hemorrhage		Diabetic ketoacidosis
Brain abscess	Cocaine			
Tetanus	Sympathomimetic poisoning (eg, amphetamines)			
Typhoid fever	Anticholinergic poisoning (eg, antihistamine)			
Malaria	Serotonin syndrome			
	Stimulant-containing dietary drugs			
	Salicylate poisoning			

*While cardiovascular disease does not directly cause heat illness, compromised cardiovascular function from underlying disease (eg, heart failure) or medication (eg, beta or calcium channel blocker) impairs a patient's ability to respond to increased environmental heat and humidity, and can contribute to heat illness.

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Graphic 53571 Version 5.0

Drugs that can cause neuroleptic malignant syndrome

Antipsychotic agents*
Aripiprazole
Chlorpromazine
Clozapine
Fluphenazine
Haloperidol
Olanzapine
Paliperidone
Perphenazine
Quetiapine
Risperidone
Thioridazine
Ziprasidone
Amisulpride
Zotepine

Antiemetic agents
Domperidone
Droperidol
Metoclopramide
Prochlorperazine
Promethazine

* This list is not complete. Virtually every antipsychotic agent has been associated with neuroleptic malignant syndrome.

Graphic 75621 Version 4.0

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