Recognizing medical emergencies- Hyperthermia

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Abstract

Hyperthermia is defined by the elevation of core body temperature above 40,5 °C, due to primary dysfunction of the thermoregulatory center in hypothalamus. It is considered a medical emergency that can lead to multi-organ dysfunction and death if not treated promptly and appropriately. The differential diagnosis is wide and the emergency medicine physicians should be aware of the main causes of febrile illness which include, except from infections and sepsis, intoxication from medication and illicit substances, neuroleptic malignant syndrome, malignant hyperthermia, endocrine disorders and environmental-related conditions. The primary goal of treatment is the decrease of core body temperature. The main cooling techniques are simple to use and should be applied in the Emergency Department immediately after the diagnosis of the condition, along with disease-specific treatment. Early recognition of the cause of hyperthermia can lead to improved outcomes in morbidity and mortality. In this topic, some of the main causes of hyperthermia will be discussed.

Key words: *Hyperthermia; drug intoxication; heat stroke; cooling techniques; surface cooling*

INTRODUCTION

Normal body temperature is approximately 37°C (degrees Celsius) or 98.6°F (degrees Fahrenheit) and varies by about 0.5°C during the day. Fever is core body temperature elevation above a "set-point" which is controlled by the thermoregulatory center in hypothalamus. This, usually, happens as a response to cytokines activated by infection or sterile inflammation [1]. On the other side, hyperthermia is a medical emergency due to complete loss of thermal control by the thermoregulatory system, leading to excessive heat generation and multi-system dysfunction [2]. The differentiating features between fever and hyperthermia can be seen in Table 1.

Core temperature (Tc) reflects the temperature of the internal organs and best describes an individual's thermal status. The measurement of Tc can be made in many sites (Table 2), but four sites are considered to give more accurate measurements of Tc, the tympanic membrane, nasopharynx, esophagus and pulmonary artery. In clinical settings the esophagus measurements are considered to be the gold standard whereas the tympanic measurements provide an alternative non-invasive technique [3].

The most common clinical manifestations of hyperthermic patients are tachypnea, tachycardia and hypotension. The skin is usually warm and in some cases sweating can be absent (hot and dry skin) [2]. Nearly every system can be impaired and the patients can present with neurologic dysfunction, such as delirium, seizures, coma etc., cardiogenic or noncardiogenic pulmonary edema, other cardiac manifestations like arrhythmias or ischemic changes, acute respiratory distress syndrome (ARDS), acute kidney injury, electrolyte and acid-base disturbances, hepatic dysfunction

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Table 1. *Differentiating features between fever and hyperthermia.*

	Fever	Hyperthermia
Temperature	Usually < 41C	>41 °C suggests hyperthermia >41,5 °C strongly indicative
Effect of antipyretics	Effective	No effect
Motor features	Rigors	Rigidity or clonus more frequently related to some forms of medication-induced hyperthermia

Table 2. *Summary of temperature measurements.*

Measurement location	Accuracy	Advantages	Disadvantages
Body surface	Low	Easy and widely available	Inaccurate
Oral	Low	Easy and widely available	Inaccurate
Axilla	Low	Easy and widely available	Inaccurate
Tympanic membrane	Satisfactory	Precise, repeatable and brain core temperature	High risk of measurement error
Rectum	Satisfactory	Easy, widely available, precise and repeatable	High latency
Urinary bladder	Satisfactory	precise and repeatable	High latency
Nasopharynx	Satisfactory	Easy, widely available	High risk of measurement error
Esophagus	Most accurate	Easy, widely available and repeatable	High latency
Pulmonary artery	Most accurate	precise and repeatable	Invasive and restricted to intensive care units

and gastrointestinal hemorrhage, rhabdomyolysis and coagulopathy or even disseminated intravascular coagulation (DIC) [4].

Causes of hyperthermia

Elevated Tc is one of the most frequently recorded vital signs among Emergency Department (ED) patients. It is difficult to differentiate between fever and hyperthermia. Fever is the main cause of elevated body temperature and is usually attributed to infection, complicated or not by sepsis or septic shock. However, if the patient's condition does not improve after the administration of fluids and antibiotics, sepsis mimics should be considered as the cause of elevated Tc. Some of these clinical conditions can be life-threatening if not treated early and appropriately. It is of great importance to identify the causes of hyperthermia (Table 3) in order to improve ED patients' outcomes [5].

1. Neuroleptic malignant syndrome

Neuroleptic malignant syndrome (NMS) is a life-threatening syndrome and it is characterized by altered mental status, hyperthermia, autonomic instability and muscle rigidity ("lead pipe" rigidity). It is associated with the use of dopamine-receptor antagonist medications but can also be precipitated by withdrawal from dopaminergic medications (e.g. those used in the treatment of Parkinson's disease). It is usually reported with the typical antipsychotics, like haloperidol and fluphenazine, but it can be caused by nearly every neuroleptic medication (including antiemetics like droperidol, metoclopramide etc). Risk factors for the development of NMS are high doses of medication, rapid escalation, and parenteral use. The syndrome can occur anytime during the course of treatment, but it usually develops within the first two weeks of the initiation of the neuroleptic agent [5][6]. The diagnosis is based on DSM-V (diagnostic and statistical manual for mental disorders) criteria:

Table 3. *Differential diagnosis of hyperthermia.*

Infection	Drug or toxin related	Neurologic	Environmental	Endocrine	Oncologic
Sepsis	Malignant hyperthermia	Hypothalamic stroke	Heat-related illnesses	Thyroid storm	Lymphoma
Meningitis	Neuroleptic malignant syndrome	Status epilepticus		Pheochromocytoma/ paraganglioma	Leukemia
Encephalitis	Withdrawal syndromes (e.g. alcohol, benzodiazepines etc.)	Intracerebral hemorrhage		Diabetic ketoacidosis	
Brain abscess	Illicit drugs (cocaine)				
Tetanus	Sympathomimetic intoxication (e.g.amphetamines)				
Typhoid fever	Anticholinergic intoxication (e.g. antihistamine)				
Malaria	Serotonin syndrome				
	Salicylate poisoning				

Major criteria (all required)

- Exposure to dopamine-blocking agent
- Severe muscle rigidity
- Fever

Other Criteria (at least two required)

- Diaphoresis
- Dysphagia
- Tremor
- Incontinence
- Altered level of consciousness
- Mutism
- Tachycardia
- Elevated or labile blood pressure
- Leukocytosis

Elevated creatine phosphokinase [6]

The standard treatment pathway for NMS comprises the discontinuation of the causative agent and supportive care including rehydration, support of the cardiopulmonary system, maintenance of normothermia and prevention of complications (e.g. heparin for deep vein thrombosis prophylaxis). Benzodiazepines, lorazepam or diazepam, can be used to control agitation if necessary. Empiric pharmacological treatment, such as bromocriptine or amantadine orally or dantrolene intravenously, has been used in more severe cases. Electroconvulsive therapy has occasionally been used in some refractory cases. ED physicians' awareness and early detection of the syndrome are crucial for the prognosis. Delayed treatment can lead to increased morbidity and fatality [6,7].

2. Serotonin syndrome

Serotonin syndrome (SS) is a potentially life-threatening condition which is frequently misdiagnosed. The most commonly implicated medications are SSRIs (Selective Serotonin Reuptake Inhibitors), linezolid and fentanyl. It can be precipitated by therapeutic medication use or intentional self-poisoning and is more frequently seen with the co-administration of the above agents [5]. The clinical presentation of SS includes autonomic instability, such as tachycardia, hyperthermia and blood pressure disturbances, neuromuscular excitation (i.e. hyperreflexia, tremor, clonus) and mental status changes like agitation, delirium and coma [8]. The physical examination can reveal other signs, such as dilated pupils, flushed skin and diaphoresis, dry mucous membranes and bilateral Babinski sign [9]. The diagnosis is based on the Hunter criteria:

Use of a serotonergic agent plus one of the following:

- Spontaneous clonus
- Inducible clonus and agitation or diaphoresis
- Ocular clonus and agitation or diaphoresis
- Tremor and hyperreflexia
- Hypertonia

Temperature >38°C and ocular clonus or inducible clonus [10]

The primary components of the emergent treatment of SS are the discontinuation of the offending medication and supportive care. The administration of intravenous (IV) fluids and oxygen, as well as the continuous cardiac monitoring and the correction of

vital signs' abnormalities constitute the mainstay of therapy. Sedation with benzodiazepines (IV lorazepam or diazepam) is used for agitation control. If agitation does not improve with the above measures cyproheptadine, a histamine-1 receptor antagonist, is suggested as an antidote [11]. If Tc is above 41,1°C, immediate sedation, paralysis, and endotracheal intubation are necessary along with the standard cooling techniques. Prognosis is in general favorable and unlike NMS (Table 4), most cases with mild to moderate symptoms resolve within 24 hours [9].

3. Malignant Hyperthermia

Malignant hyperthermia (MH) is a progressive, hypermetabolic, life-threatening reaction caused by the exposure to a volatile anesthetic (e.g. halothane, isoflurane etc.) or succinylcholine. A genetic disorder of skeletal muscle receptors is the abnormality that leads MH-susceptible persons receiving general anesthesia to result in excessive muscle contraction, rhabdomyolysis, anaerobic metabolism and acidosis [12,13]. The most frequent initial clinical signs that usually develop within minutes after the administration of the offending anesthetic, are hypercarbia (elevated end-tidal CO2), tachypnea and sinus tachycardia. Hyperthermia often occurs later on the course of MH reaction, along with generalized muscle rigidity, masseter muscle rigidity and arrhythmias [14,15]. Treatment of MH consists of the immediate discontinuation of the anesthetic, the optimization of oxygenation and ventilation, management of cardiac arrhythmias, the administration of intravenous dantrolene and correction of laboratory and acid-base abnormalities. Cooling techniques can be used for patients with Tc above 39 °C [16]. Awareness should be raised among emergency medicine physicians to the possibility of fatal non-anesthesia triggered MH episodes in MH-susceptible persons. People with the genetic disorder can present with similar to MH clinical features after exposure to thermal stress, including febrile illness or exercise. This disorder is characterized as "non-anesthetic" or "awake" malignant hyperthermia and it is usually resolved spontaneously or after the administration of low dose of oral dantrolene (i.e. 25 mg orally) [17,18].

4. Salicylate toxicity

The best-known salicylate is acetylsalicylic acid (aspirin). Patients with salicylate toxicity will present with high body temperature, tachycardia, tachypnea and lactic acidosis. Acidosis is caused by the interference of salicylate with the anaerobic metabolism. The acid-base changes that are observed in these cases are firstly respiratory alkalosis due to centrally mediated hyperventilation, subsequently compensatory non-gap metabolic acidosis and finally anion-gap metabolic acidosis due to lactate accumulation. The classic triad of symptoms includes hyperpnea, tinnitus and gastrointestinal irritation. With the progression of metabolic acidosis, the patient deteriorates, and severe complications arise such as pulmonary edema, CNS (Central Nervous System) depression and even death. Aggressive treatment may be needed in the emergency department like volume resuscitation, airway management, systemic alkalinization with sodium bicarbonate and hemodialysis [5,19,20].

5. Anticholinergic toxicity

Anticholinergics are among the most frequently reported drugs that can be associated with non-pyrogenic hyperthermia and heat-related mortality in the elderly [21]. They can interfere with the ability to sweat by the inhibition of muscarinic receptors on the sweat glands resulting in anhidrotic hyperthermia [5]. Antihistamines, tricyclic antidepressants and recreational drugs can lead to the development of an anticholinergic toxidrome with dry mucous membranes, dilated unreactive pupils, paralytic ileus and urinary retention, as long as symptoms from the CNS like agitation that can progress to

Table 4. *Distinguishing features between NMS and SS.*

	Serotonin syndrome (SS)	Neuroleptic Malignant syndrome (NMS)
Onset	Within 24 h	Days to weeks
Neuromuscular findings	Hyperreactivity (tremor, clonus)	Bradyreflexia, severe muscular rigidity
Causative agents	Serotonin agonists	Dopamine antagonists
Treatment agents	Benzodiazepines, cyproheptadine	Bromocriptine, dantrolene
Resolution	Within 24 h	Days to weeks

delirium [22]. Physostigmine, a cholinesterase inhibitor, is used as an antidote for the treatment of anticholinergic delirium. Benzodiazepines can be used for agitation and seizures along with supportive care [5,22].

6. Sympathomimetic toxicity or withdrawal from sympathetic antagonists

Illicit sympathomimetic drugs, such as cocaine, amphetamines, methylenedioxymethamphetamine (MDMA), can cause severe toxicity due to increased adrenergic response. Hypertension, tachycardia, dilated but reactive pupils (unlike anticholinergic toxicity) (Table 5), psychomotor agitation and hyperthermia. The degree of hyperthermia is related to the mortality rate. The goal of treatment is to control the excessive adrenergic stimulation and agitation. Benzodiazepines are the mainstay of treatment, and they are titrated to the desired effect. In more severe cases, the addition of a nondepolarizing neuromuscular blocker may be necessary. Cooling techniques for passive and active cooling, depending on the severity of hyperthermia, can be used for further thermal control [23].

Withdrawal from alcohol or benzodiazepines can result in excessive sympathetic activity. Symptoms from benzodiazepines withdrawal usually develop between 2-10 days after the discontinuation of the drug, while symptoms from alcohol withdrawal manifest within the first 48-72 hours since the last alcohol consumption [24]. Clinical manifestations of benzodiazepine withdrawal vary from mild symptoms, like muscle-spasms, pain, anxiety and panic disorders, to more severe symptoms like disorders of perception, hallucinations, autonomic disturbances, seizures and delirium [25]. Minor alcohol withdrawal symptoms include tremulousness, diaphoresis, anxiety and palpitations. In more severe cases, patients develop seizures, alcoholic hallucinosis and delirium tremens [26]. In both situations, the administration of benzodiazepines is the treatment of choice and large doses may be needed until the desirable level of sedation and control of symptoms is achieved [24,27,28].

7. Thyroid storm

Thyroid storm, the most severe form of thyrotoxicosis, is considered a medical emergency. One in every six patients presenting with symptoms of thyrotoxicosis has a final diagnosis of thyroid storm. It has a high mortality rate, about 12-fold higher than in hospitalized patients with thyrotoxicosis without thyroid storm [29][30]. Other acute circumstances, such as infection, trauma, surgery, myocardial infarction, can precipitate this condition. Clinical manifestations may include hyperthermia, cardiac arrhythmias, gastrointestinal disorders and impaired mental status [30]. Other findings from the clinical presentation include ophthalmopathy, lid-lag, hand tremor and hyperreflexia [5]. Very low or undetectable TSH is the basic laboratory abnormality, but several diagnostic scores like the Burch-Wartofsky score or the Akamizu criteria have been proposed as adjuncts to the diagnosis [31]. Management of thyroid storm includes the administration of antithyroid drugs (propylthiouracil and methimazole), saturated solution of potassium iodide, hydrocortisone to decrease the conversion of T4 to T3 and beta-blockers for the relief of symptoms caused by the increased adrenergic activity. Supportive care with intravenous fluids, oxygen and cooling techniques is also essential, as well as treatment of precipitating factors [30].

8. Heat stroke

Heat-related illnesses are divided into three main

Table 5. *Differentiating features between sympathomimetic and antiholinergic toxidrome on physical examination.*

Organ system	Sympathomimetic	Anticholinergic
Ocular	Dilated and reactive pupils	Dilated and nonreactive pupils
Oral mucosa	Wet	Dry
Respiratory	Bronchodilator	Bronchodilator
Cardiovascular	Elevated blood pressure and tachycardia	Elevated blood pressure and tachycardia
Gastrointestinal	Normal bowel sounds	Decreased/absent bowel sounds
Genitourinary	Normal urination/occasionally urinary retention	Urinary retention
Skin	Diaphoretic	Red and dry
Neurologic	Psychomotor agitation	Hallucinations

categories. Minor heat illness (i.e. heat cramps, heat edema, heat syncope and prickly heat), heat exhaustion and heat stroke [2]. The clinical presentation depends on the body's ability to cope with heat. Heat stroke is the most severe illness and is defined on the basis of Tc > 40°C and neurologic dysfunction. There are two forms of heat stroke, the exertional and nonexertional. The exertional heat stroke is usually recognized in young individuals such as athletes, street workers and military recruits, who engage strenuous activity for a prolonged period of time in hot and dry environment [32,33]. In one study, the investigators observed that there was a 54% increase in risk for a work-related hyperthermia ED visit during an extreme heat event [34]. The classic nonexertional heat stroke usually affects the elderly or very young individuals and people with comorbidities during environmental heat waves. In most cases, it is attributed to the lack of adequate hydration and air conditioning. The presentation in these cases may be subtle and a high index of suspicion is required for the diagnosis [32]. During the next years, the number of ED visits, hospitalizations and deaths by heat stroke is expected to increase due to global warming [33]. There are several categories of people at greater risk of developing heat related illness (Table 6) [35].

When Tc is elevated, sweat production and cardiac output increase and heat dispersion through the skin is enhanced due to cutaneous vasodilation and visceral vasoconstriction. As these compensatory mechanisms fail and thermal homeostasis is disturbed, circulatory collapse emerges with catastrophic manifestations in multiple organs [4,35]. Typical symptoms include, except from hyperthermia and altered mental status, tachypnea, tachycardia, hypotension and hot, dry skin with absence of sweating. It can be complicated by myocardial ischemia, arrhythmias, rhabdomyolysis, acute kidney injury (AKI), acute hepatic failure, disseminated intravascular coagulation (DIC), gastrointestinal bleeding and electrolyte disturbances [2,4].

The diagnostic testing includes fingerstick glucose, complete blood count differential, coagulation testing, serum labs for the evaluation of electrolytes, renal and hepatic function, creatine kinase (CK) and cardiac biomarkers, urinalysis and electrocardiogram (ECG). Chest X-Ray, blood cultures, medication levels (if intoxication is suspected), neuroimaging, thyroid hormone levels etc. can be useful for the differential diagnosis [2,32]. Bedside ultrasound may assist in the estimation of ventricular filling and volume status [35].

The mainstay of treatment is rapid reduction of the Tc to about 39 °C because the duration of hyperthermia is related with the prognosis and the patient's outcome. However, the general measures, including insertion of two large bore intravenous catheters, rehydration, continuous cardiac and core temperature monitoring, administration of supplemental oxygen and early airway management, are of great importance. If the hemodynamic status is not supported adequately the risk of death and disabling neurological damage is higher [2,33,35]. Fluid replacement must be sufficient to restore hypotension and tissue perfusion. Due to lack of evidence for more specific recommendations (i.e. the type of fluid, the rate and volume of infusion), the therapeutic approach of fluid management in sepsis can be used as a guide to heatstroke because of the pathophysiological similarities between the two conditions [36]. The usual recommendation is that at least 30 ml/kg of IV crystalloids should be given within the first three hours. The

Table 6. *Risk factors for heat related illness.*

Non-modifiable risk factors	Modifiable risk factors
Age (the elderly and children)	Dehydration
Autonomic diseases with anhidrosis (Ross syndrome, Sjögren syndrome)	Prolonged activity in hot and humid environment
Spinal cord injuries	Occupational categories (military staff, athletes, outfield employees etc.)
Endocrine disorders (Diabetes, hyperthyroidism)	Abuse (alcohol, cocaine, amphetamine, opioids, etc.)
Neurological disorders (epilepsy)	Drugs (anticholinergics, beta-blockers, diuretics, neuroleptics, anesthetics)
Dermatological diseases (scleroderma, burns)	Infections
Hereditary disease (malignant hyperthermia)	Obesity

fluid resuscitation can be guided by the serum lactate level and the capillary refill time (CRT) as adjuncts to evaluate tissue perfusion, while dynamic measures including passive leg raising and cardiac output (CO) measurement can provide more accurate information [37]. The control of agitation is very important because the continuous muscle activity leads to further heat production, and it also increases the risk of rhabdomyolysis. So, the sedation of the agitated patient may be necessary regardless of whether the patient is intubated or not. Benzodiazepines are the first-line treatment of agitation, especially in cases of concurrent intoxication, as they act as muscle relaxants and because of their anti-seizure effect. Other options for sedation can be ketamine, propofol, opioids and dexmedetomidine. Benzodiazepines are also used for the suppression of shivering, which can impair temperature management if not controlled. If the patient is already intubated, paralysis with a non-depolarizing muscle-relaxant may be used for the treatment of shivering. Indications for intubation include the need for diagnostic procedures (i.e. lumbar puncture) in patients with altered mental status, status epilepticus, severe rigidity and the usual indications such as respiratory failure, refractory agitation etc. [32,33].

Cooling techniques

There are several methods of cooling. The choice of cooling technique depends on available resources and the cause of hyperthermia. The only absolute contraindication to cooling is a normal or low temperature. In cases of hyperthermia due to causes other than heat stroke, disease-specific treatment should not be delayed. Despite the method chosen, all clothes should be removed, and the patient should be totally exposed. The core temperature should be continuously monitored, and active cooling should be discontinued when Tc reaches 38-39 °C in order to avoid overshoot hypothermia. An esophageal or bladder probe is preferred but rectal temperature may be measured if the other options are unavailable. The standard equipment in an ER for the different techniques includes sheets/towels, a body bag, a cooling blanket, cold saline, ice packs, cool water bath, foley catheter, spray bottle and a fan [32,38].

1. Surface cooling

Surface cooling is the most important technique. An immersive ice-bath is considered to be the gold-standard for rapid cooling (achieving rates of cooling ~0.2 °C per minute). The technique includes filling a bath of water with ice until the water reaches a temperature of as low as 1-17 °C prior to the patient's immersion (true ice-water immersion). If the ice bath is not available, the patient can be placed in a body bag (or plastic sheets), which is filled with water and ice and then the body bag is closed up to the patient's neck. An alternative method of surface cooling is the evaporative cooling (cooling rates of ~0.1 °C per minute). The patient is sprayed with lukewarm water and then a fan is placed directly to the patient. A cooling blanket underneath the patient and ice packs on the groin, axilla and neck can be also used in order to maximize heat loss [32,39,40].

2. Internal cooling

Surface cooling is in general very effective but in patients presenting with shock can be delayed due to peripheral vasoconstriction. In such patients internal cooling using refrigerated crystalloid at 0-4 °C is beneficial. Although cooled fluids have not been studied in hyperthermia, their efficacy has been well established in other situations such as anesthesiology and neurocritical care [32]. The amount of IV fluids should be titrated with continuous core temperature measurement and patients with comorbidities, such as heart, liver or kidney failure, need special attention. Each 30 ml/kg bolus of 4 °C crystalloid is expected to reduce Tc by ~1,2-1,4 °C in hyperthermic patients, whereas the same dose of 20 °C crystalloid is expected to reduce Tc by 0,6-0,9 °C [41].

Other cooling methods are respiratory cooling (for short-term use) or more invasive methods like cold gastric, rectal or peritoneal lavage [35].

All patients should be hospitalized in order to be stabilized and observed for potential complications for at least 24 hours. Critically ill patients may worsen during cooling. In addition, skin is susceptible to damage from prolonged exposure to ice so it should be frequently checked during the cooling process. Close monitoring to avoid shivering that can impede cooling efforts, as well as hypothermia and its sequelae is crucial [42].

CONCLUSIONS

Hyperthermia may be difficult to diagnose in the emergency department setting. A great effort should be made so as all useful information is obtained regarding past medical and family history, drug history and the description of the event. A source of infection should be investigated in all cases with elevated body temperature but if the patient does not respond

to treatment with fluids and antibiotics emergency medicine physicians should seek for other causes of hyperthermia. The decrease of body core temperature is the most critical intervention in hyperthermic patients and along with disease-specific treatment, it should start as soon as possible in order to improve prognosis. Among cooling techniques, the immersive ice bath is considered the gold standard but other methods of surface cooling, which are simple to use, can be applied in the emergency department by an interprofessional team.

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