Diagnosis and Management of Heatstroke

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ABSTRACT

Heatstroke is a life-threatening and the most severe form of heat-related illnesses, characterized by body temperature >40°C and central nervous system dysfunction. Heatstroke is classified into Non-Exertional Heatstroke (NEHS) and Exertional Heatstroke (EHS). The pathophysiology of heatstroke involves a combination of direct heat effects on the host, the systemic inflammatory and coagulopathic response. The diagnosis of heatstroke based on Bouchama’s definition or Japan Association of Acute Medicine (JAAM) criteria. The basic principle of heatstroke management is early resuscitation and immediate cooling. Cold water immersion or convection evaporation method can be implemented based on the specific patient characteristic. Preventive strategies are early recognition by health workers, socialization to vulnerable groups and adequate acclimatization.

Keywords: diagnosis, management, heatstroke.

INTRODUCTION

Heatstroke is the severe form of heat-related illnesses, characterized by body temperature >40°C and central nervous system dysfunction.¹ The mortality rate is 10-30% and 7-20% of patients who survive suffer from permanent neurological damage.² The risk of heatstroke is influenced by both intrinsic and extrinsic factors.³⁴ Heatstroke is classified into two types based on heat exposure, namely Non-Exertional Heatstroke (NEHS) and Exertional Heatstroke (EHS). Non-Exertional Heatstroke is caused by exposure to exogenous ambient temperatures and high humidity, whereas EHS is caused by endogenous exposure to excessive heat production after heavy physical activity.¹⁵

The pathophysiology of heatstroke involves a combination of direct heat effects on the host,
the systemic inflammatory and coagulopathic response. The diagnosis of heatstroke relies on the application of the definition criteria and the recognition of clinical signs and symptoms. Laboratory investigations are not necessary to confirm or exclude the diagnosis. The principle management of heatstroke is resuscitation and immediate cooling in various ways to have a better patient prognosis.

**EPIDEMIOLOGY**

In 2003 more than 15,000 deaths from heatwaves were reported in France. At least 600 children died of heatstroke after being left in a car during 1998-2013 in America. Exertional Heatstroke was reported as the third leading cause of death after a heart attack and head neck trauma. The mortality rate of heatstroke in the United States was reported around 3332 in 2006-2010. In 2050, the mortality rate is expected to increase by 2.5 times.

Non-Exertional Heatstroke more often affects infants or elderly with chronic diseases because they are unable to control the environment and fluids consumption. Children are more prone to suffer from NEHS because the body surface area ratio compared to body mass is greater than adults. The elderly are very susceptible to heat-related illnesses due to decreased blood flow to the skin, reduced sweat gland function, cardiac output, thirst sensation, and kidney function. Besides, the elderly often consume a lot of routine drugs, lower body fluid volume, and protective protein loss due to aging.

In the elderly population, a study shows that lying in bed, not leaving the house every day, unable to take care of themselves, psychiatric, cardiovascular, and lung disorders are associated with the risk of death in NEHS.

Exertional Heatstroke usually occurs in young and healthy individuals, such as military personnel, firefighters, and athletes who participate in heavy tournaments at hot temperatures. Female gender is a protective risk factor for EHS. Besides the protective effect of the hormone estrogen, the female has lower triggers for thermoregulation and less muscle mass than men. Risk factors of EHS can be intrinsic or extrinsic. Intrinsic factors include lack of acclimatization, previous febrile illness, skin disorders, dehydration, drugs, lack of sleep, alcohol use, obesity, cardiovascular disorders, and poor fitness. Extrinsic factors include hot and humid environments, excessive physical exercise, unbalanced work-to-rest ratios, heavy clothing, lack of education, and absence of emergency plans to prevent or treat heatstroke.

Some factors that influence prognosis of heatstroke are the duration of hyperthermia, speed of temperature decrease, and the level of organ damage. Recovery is seen more quickly in patients with EHS with death rates around 3-5%, lower than NEHS at 10-65%. When the initial temperature is 42.2°C, the death rate reaches 80% and it becomes zero once body temperature decrease to 38°C within 30 minutes.

**PATHOPHYSIOLOGY**

Heatstroke occurs due to a combination of direct heat effects on the host, the systemic inflammatory and coagulopathic response. Body temperature is maintained normally at 36.6-37.2 °C through a mechanism called thermoregulation. The maximum critical limit for the human body is the temperature of 41.6°C. Humans can survive at a temperature of 42°C in just 45 minutes to 8 hours. At extreme temperatures 49-50°C, cell necrosis occurs in less than 5 minutes. Excessive heat, usually temperatures >42.2°C cause protein denaturation, destabilization of phospholipids and lipoproteins, cell damage, and multiorgan failure. Thermoregulation is controlled by the hypothalamus and the autonomic nervous system through several physiological process. Heat loss is common through 4 mechanisms, namely conduction, convection, radiation, and evaporation. Conduction is heat loss through direct contact between objects, only 3% of heat loss. Convection is heat loss through moving fluid or air, about 12-15% of heat loss. Radiation is heat loss through electromagnetic waves, contributing the most to heat loss which is 55-65%. Evaporation is the heat loss through changing water into steam, which about 25% of heat loss.

When body temperature rises, the anterior hypothalamic preoptic nucleus stimulates the
Efferent of the autonomic nervous system results in peripheral vasodilation, increased blood flow of the skin, and sweating. Evaporation is the main heat loss mechanism in hot environments, but this method becomes ineffective when humidity is above 75%. The process of sweating can remove salt and liquid up to 2 liters of water. Loss of salt and water through sweating causes dehydration and salt deficiency associated with muscle cramps. Peripheral vasodilation causes a relative decrease in intravascular volume, decrease visceral perfusion, and results in heat syncope. Decreased visceral perfusion leads to endotoxin leakage into the systemic circulation. Endotoxins can activate endothelial cells and leukocytes by releasing various cytokines such as interleukin-1 (IL-1), interleukin-6 (IL-6), and high-mobility group box 1 proteins (HMGB1) which are markers of cell and tissue damage.

The human body has a protective mechanism against heatstroke that is mediated by a specific protein. Heat Shock Protein (HSP) is a protein produced by almost all cells due to responses to stress conditions including exposure to heat or cold. There are two cytoprotection mechanisms of HSP. First, a molecular chaperone, where HSP binds to proteins in a folded state, preventing expansion and denaturation. Also, HSP repairs damage caused by hyperthermia. Second, HSP regulates central baroreceptor reflexes during the heat exposure process. The coagulation response that occurs in heatstroke arises due to endothelial activation. Heat endothelial damage is thought to cause the effects of platelet aggregation and microvascular thrombosis, which triggers consumptive coagulation. Paradoxical bleeding can occur because of decreased platelet counts and inhibition of platelet release from the bone marrow. The final common complications are ventricular fibrillation, disseminated intravascular coagulation (DIC), and multiple organ failure.

**DIAGNOSIS OF HEATSTROKE**

Heat-related illnesses usually occur in normal people who are exposed to hot weather for a short time. These conditions include heat rash, heat edema, heat cramps, heat exhaustion, and heatstroke. Heat exhaustion is milder than heatstroke that indicates the inability to continue activities due to hot environmental conditions. Body temperature can be normal or slightly increase around 37-40°C. The symptoms and signs include discomfort, extreme thirst, anxiety, headache, weakness, nausea, vomiting, diarrhea, pale skin, tachycardia or hypotension, and syncope. The two most susceptible organ to extreme body temperature are the brain (cerebellum) and the liver. The involvement of these two organs distinguishes heat exhaustion and heatstroke.

A history of exposure to a hot environment is crucial in the diagnosis of heatstroke. Patients complain of dizziness, weakness, lethargy, irritability, nausea, vomiting and seizures. Body temperature usually ranges from 40-44°C, where most patients present with temperatures >42°C. The current definition of heatstroke is based on Bouchama, i.e. core body temperature >40°C accompanied by dry skin and central nervous system disorders such as delirium, seizures or coma. This condition is related to the systemic inflammatory response that results in organ dysfunction syndrome with predominant encephalopathy. Another diagnostic criteria for heatstroke developed by The Japanese Association for Acute Medicine in 2016 was patients exposed to a hot environment accompanied by one of GCS <14, creatinine or total bilirubin >1.2 mg/dL and JAAM DIC score >4. The comparison of Bouchama’s definition and JAAM criteria can be seen in Table 1, and the differences between NEHS and EHS showed in Table 2.

Central nervous system dysfunction is characterized by decreased consciousness, speech disorder, irritability, agitation, ataxia, decreased coordination, opisthotonus, hallucinations, delirium, convulsions, and coma. Central nervous system disorders occur due to a combination of cerebral edema, ischemia, metabolic disorders, and endogenous pyrogen release. On a head CT scan, diffuse brain edema might appear after 3-5 days. Areas of the brain that are generally affected are the cerebellum, hippocampus, brain stem, and thalamus.
out central nervous system infections, if it is difficult to exclude by history taking and physical examination.\(^\text{18}\)

Cardiovascular dysfunction includes hypotension, tachycardia, arrhythmias, and shock.\(^\text{7}\) Hypotension occurs due to a combination of dehydration and peripheral vasoconstriction. Circulatory shock occurs in 20-65% of cases, mainly distributive in nature, characterized by high cardiac index, low vascular resistance, and organ perfusion defects.

Table 1. Comparison of Bouchama’s definition and the JAAM criteria for heatstroke.\(^\text{9}\)

<table>
<thead>
<tr>
<th>Environment</th>
<th>Bouchama’s definition</th>
<th>JAAM criteria</th>
<th>JAAM-HS-WG criteria</th>
</tr>
</thead>
<tbody>
<tr>
<td>Core body temperature &gt; 40°C</td>
<td>Exposure to environmental heat (classic heatstroke)</td>
<td>Exposure to high environmental temperature</td>
<td>-</td>
</tr>
<tr>
<td>Body temperature</td>
<td>Impaired consciousness; JCS &gt; 2; cerebellar symptoms, convulsive seizures</td>
<td>GCS score &lt; 14</td>
<td>-</td>
</tr>
<tr>
<td>Organ dysfunction</td>
<td>Central nervous system</td>
<td>Delirium, convulsions, or coma</td>
<td>-</td>
</tr>
<tr>
<td>Coagulation</td>
<td>-</td>
<td>Diagnosed as DIC by JAAM</td>
<td>JAAM DIC score &gt; 4</td>
</tr>
<tr>
<td>Liver</td>
<td>-</td>
<td>Follow-up after admission to hospital, hepatic or renal impairments requiring inpatient hospital care</td>
<td>Creatinine or total bilirubin levels &gt; 1.2 mg/dL</td>
</tr>
<tr>
<td>Renal</td>
<td>-</td>
<td>-</td>
<td>-</td>
</tr>
<tr>
<td>Cardiovascular</td>
<td>-</td>
<td>-</td>
<td>-</td>
</tr>
<tr>
<td>Respiratory</td>
<td>-</td>
<td>-</td>
<td>-</td>
</tr>
</tbody>
</table>

GCS, Glasgow Coma Scale; JAAM, Japanese Association of Acute Medicine; JAAM-HS-WG, Japanese Association of Acute Medicine heatstroke committee working group; JCS: Japan Coma Scale; DIC, disseminated intravascular coagulation.

Table 2. Comparison of NEHS versus EHS.\(^\text{19}\)

<table>
<thead>
<tr>
<th>Characteristics</th>
<th>NEHS</th>
<th>EHS</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age</td>
<td>Very young, elderly</td>
<td>Young (15-50 years), healthy</td>
</tr>
<tr>
<td>Health</td>
<td>Often chronically ill</td>
<td>Typically healthy</td>
</tr>
<tr>
<td>Febrile illness</td>
<td>Unusual</td>
<td>Common</td>
</tr>
<tr>
<td>Weather condition</td>
<td>Heat wave</td>
<td>Temperate or hot</td>
</tr>
<tr>
<td>Activity</td>
<td>Sedentary</td>
<td>Sustained or heavy exertion</td>
</tr>
<tr>
<td>Medications or drug use</td>
<td>Diuretics, beta blockers, antihistamines, antidepressants</td>
<td>Ergogenic aids, ecstasy, cocaine</td>
</tr>
<tr>
<td>Sweating</td>
<td>Often absent</td>
<td>Often present</td>
</tr>
<tr>
<td>Acid-base disturbance</td>
<td>Mixed respiratory alkalosis and metabolic acidosis</td>
<td>Severe metabolic acidosis</td>
</tr>
<tr>
<td>Calcium</td>
<td>Normal</td>
<td>Hypocalcemia</td>
</tr>
<tr>
<td>Potassium</td>
<td>Normal</td>
<td>Hyperkalemia; hypokalemia (~30%)</td>
</tr>
<tr>
<td>Phosphate</td>
<td>Hypophosphatemia</td>
<td>Hyperphosphatemia</td>
</tr>
<tr>
<td>Blood glucose</td>
<td>Hypoglycemia</td>
<td>Hyperglycemia</td>
</tr>
<tr>
<td>Rhabdomyolysis</td>
<td>Rarely severe</td>
<td>Often severe</td>
</tr>
<tr>
<td>Acute renal failure</td>
<td>Uncommon (~5%)</td>
<td>Common (~25%)</td>
</tr>
<tr>
<td>DIC</td>
<td>Mild</td>
<td>Severe</td>
</tr>
<tr>
<td>CK</td>
<td>Mild elevation</td>
<td>Marked elevation</td>
</tr>
<tr>
<td>AST, ALT</td>
<td>Mild elevation</td>
<td>Marked</td>
</tr>
</tbody>
</table>

CK, creatinine kinase; AST, aspartate aminotransferase; ALT, alanine aminotransferase; DIC, disseminated intravascular coagulation.
resistance, and normal or low filling pressure.\textsuperscript{2,5} Electrocardiogram abnormality occurs in 85% of heatstroke cases, where sinus tachycardia is around 43-79% and QT interval prolongation is about 61%.\textsuperscript{1} This heart disorder may be caused by an increase in catecholamines due to stress-induced cardiomyopathy.\textsuperscript{3,16}

Kidney disorders in heatstroke are multifactorial due to hypovolemia, rhabdomyolysis, and DIC.\textsuperscript{1} Rhabdomyolysis occurs in 25-30% of EHS and 5% of NEHS cases. The sign and symptoms are muscle aches, muscle stiffness, muscle weakness, dark brown urine, oliguria, and anuria.\textsuperscript{7} Low potassium can cause cardiovascular disorders and decrease blood flow to the muscles making it easier for rhabdomyolysis.\textsuperscript{4,16}

Respiratory disorders can range from shortness of breath, cyanosis to ARDS.\textsuperscript{7} In EHS patients, blood gas analysis shows respiratory alkalosis at first then develops into metabolic acidosis. Whereas in NEHS patients, there is isolated respiratory alkalosis or a mixture of respiratory alkalosis and metabolic acidosis in 60% of patients.\textsuperscript{1,5}

Liver dysfunction is characterized by an immediate increase in transaminase and lactate dehydrogenase which peak at days 3-4. Bilirubin increases more slowly, around 24-27 hours after the onset of heatstroke. Liver dysfunction might result from direct heat effects, decreased splenic blood flow, and hepatocyte injury. Reduced ability of the liver to detoxify endotoxins increase the number of endotoxins in the blood.\textsuperscript{1,7,17}

Coagulopathy disorders cause skin bruising, ecchymosis, conjunctival bleeding, haematochezia, melena, hemoptysis, haematuria, myocardial bleeding, and intracranial hemorrhage.\textsuperscript{7,16,17} Disseminated Intravascular Coagulation can occur in 45% of heatstroke, which characterized by low platelets, low hemoglobin, prolong prothrombin, and thromboplastin time, increased D-dimers and low fibrinogen.\textsuperscript{7,17}

In principle, there is no single laboratory test that can confirm or exclude the diagnosis of heatstroke. Laboratory investigations include complete blood count, kidney function, liver function, and electrolytes.\textsuperscript{7,14,16} Laboratory features that support the diagnosis of heatstroke include leucocytosis, can reach 30-40x103/mm\textsuperscript{3}, increased urea and creatinine with hemogranular cast, proteinuria, increased serum transaminases, increased creatinine kinase, myoglobinuria, hyponatremia, metabolic acidosis, and respiratory alkalosis.\textsuperscript{16} Polycythaemia, hypercalcaemia, and hyperalbuminemia are due to dehydration. The condition of hypokalaemia and hypophosphatemia result from loss of perspiration, the effects of catecholamines, and hyperventilation.\textsuperscript{1} Hyperglycaemia is often associated with NEHS, whereas hypoglycemia, although rarely, tends to occur in EHS.\textsuperscript{6}

The clinical features of heatstroke can mimic other medical conditions such as meningitis, encephalitis, malaria, malignant neuroleptic syndrome, hyponatremia, septic shock, thyroid crisis, acute myocardial infarction, malignant hyperthermia, and drug use or reactions.\textsuperscript{2,15,18,19} Hyponatremia can be distinguished from heatstroke by the history of excessive fluid consumption, normal pulse, normal body temperature, polyuria, and normal or hypertension.\textsuperscript{1} Malignant hyperthermia results from increased heat production by muscle hypermetabolism after exposure to anesthetic drugs. Whereas malignant neuroleptic syndrome is an idiosyncratic reaction to dopamine antagonists, cause a combination of muscle activity and inhibition of heat loss.\textsuperscript{5} Toxicological screening is useful to exclude drugs that can cause hyperthermia such as ethanol, amphetamines, cocaine, salicylates, hallucinogens, and lithium.\textsuperscript{16}

**MANAGEMENT OF HEATSTROKE**

The treatment goals of heatstroke are vital signs returned to normal, volume status euvolemic, full consciousness, laboratory results improved and no complications.\textsuperscript{16} The management begins with airway stabilization, breathing, and circulation. Move the patient immediately to a shaded environment, lye the patient down on the flat surface and remove clothing as necessary.\textsuperscript{2,7} If there are no life-threatening complications, cooling immediately at the scene.\textsuperscript{10} Cooling should be done at the “golden half-hour” after the patient is unconscious, following the principle
of “cool first, transport second”.

A decrease in the patient’s body temperature can be achieved in three ways namely conduction, evaporation, and convection. When transporting the patient, give oxygen supplementation of 3-5 L/min and maintain oxygen saturation above 90%, turn on air conditioner and open the window of the ambulance, adjust the room temperature to 20-24°C.

Conduction can be achieved by applying an icepack or wet towels on the neck, armpits, and groin. Coldwater immersion is the most effective conduction cooling method and is recommended by The National Athletic Trainers’ Association and the American College of Sports Medicine as the treatment choice of EHS. Coldwater immersion decreases body temperature most rapidly at 0.15-0.35°C per minute but has side effects of chills and peripheral vasoconstriction. The cold water immersion method is faster, safer, and effective for young patients, athletes, and military members who experience EHS. During the cooling process, massage the entire body to prevent vasoconstriction.

Evaporation can be done by spraying the skin with tap water at 25-30°C. Convection is carried out by increasing the air velocity of the skin using a fan. Evaporation and convection method which is performed by spraying cold water of 15°C to the patient’s skin and at the same time blow warm air around the body, can reduce body temperature 0.05-0.09°C per minute in adults. For elderly patients with comorbidities, this method is better, because the cold water immersion renders vascular access and monitoring measures in elderly patients.

Currently, there is no evidence of what is the target of body temperature in the management of heatstroke, but the rectal temperature of 39.4°C (38-39°C) has been used in many studies. Other body temperature target is 39°C within 10-40 minutes and <38.5°C in the first 2 hours. During the cooling process, skin temperature should be maintained 30-34°C to avoid peripheral vasoconstriction and chills.

No pharmacological therapy has been proven effective in the management of heatstroke. Avoid using aspirin or acetaminophen because it can cause liver, kidney problems, and worsen coagulopathy. Salicylates can also worsen hyperthermia through the release of phosphorylation oxidation. Dantrolene is a drug that works by inhibiting the release of calcium ions from the endoplasmic reticulum, thereby reducing muscle rigidity and hypertonicity. This drug is indeed useful for cases of malignant hyperthermia and malignant neuroleptic syndrome but there is no supporting evidence for use in cases of heatstroke.

In case of hypotension, initial therapy is 250-500 ml crystalloid bolus infusion. If it is not responded, continued with dopamine administration at an initial dose of 3-10 µg/kg/min, that can be increased to 20 µg/kg/min depending on vital signs and measurement of central venous pressure. The use of alpha-adrenergic vasopressors should be avoided because it theoretically can exacerbate peripheral vasoconstriction, inhibit a decrease in core body temperature.

The complications of rhabdomyolysis can be overcome by giving intravenous fluids based on hemodynamic conditions, alkalinization of urine, and mannitol infusion. Administer crystalloid fluid with a urine target of 3 cc/kg BW/hour or 200-300 ml/hour, the amount of fluid can be up to 6-10 L/day. If the amount of urine volume is not on target, furosemide can be added 10-20 mg. Supplementation of sodium bicarbonate can be given to reach a urine pH >6.5 inhibiting the precipitation of myoglobin in the kidney tubules.

Prophylactic antibiotics such as the second generation of cephalosporin can be given to prevent infection. In the conditions of anxiety, chills, and seizures, strong sedatives that act quickly, effectively, and minimal side effects such as propofol and benzodiazepines can be given to the patients. Corticosteroids are only indicated in conditions of persistent fever >39°C accompanied by some consolidation or shadow on chest x-ray which worsens quickly and meets the diagnostic criteria for ARDS.
types and doses of steroids that can be given are dexamethasone 7.5 mg/day, hydrocortisone 200 mg/day or methylprednisolone 80-120 mg/day.\(^7\)

**PREVENTION**

The condition of heatstroke is easier to prevent than to treat.\(^17\) Methods of preventing heatstroke are the use of air conditioners, limiting outdoor activities during the day, adequate fluid consumption, using loose and brightly colored clothing,\(^10\) carefully using drugs that can cause fluid loss, and avoid leaving children in the car alone.\(^9,23\) Acclimatization is a physiological adaptation process that is very important in the new environment. Acclimatization in hot environments takes about 7-14 days, although it can take up to 2 months. Optimal acclimatization requires physical exercise with a certain intensity so that body temperature rises 38.5 °C for at least 60 minutes. Individuals who are not acclimatized can only produce 1 L of sweat per hour, equivalent to 580 kcal/hour, while individuals who are acclimatized can produce 2-3 L of sweat per hour, equivalent to 1740 kcal/hour.\(^13\) The adaptation process will lead to some physiological effects such as a decrease in the threshold of sweating, increased sweat production, increased skin blood flow, decreasing the concentration of salt in the sweat, the lower core body temperature when doing standard physical training, and the expansion of intravascular volume.\(^1,14,16,24\)

**CONCLUSION**

Heatstroke is a life-threatening condition that is caused by the body’s failure to remove the heat at high ambient temperatures or excessive body heat production with heat loss failure in heavy physical exercise. There are two types of heatstroke, i.e. NEHS, which often affects children or elderly with comorbidities and EHS, which strikes young people, athletes or military personnel. Heatstroke results from a combination of direct heat injury, systemic inflammatory and coagulopathy response. The diagnosis of heatstroke is based mainly on clinical criteria. The management is immediate resuscitation and early decrease in body temperature. Preventive strategies are the education of health workers to diagnose this condition early, socialization to vulnerable groups and adequate acclimatization.

**ACKNOWLEDGMENTS**

We would like to thank the Dean of Faculty of Medicine, University of Mataram, and the Director of West Nusa Tenggara General Hospital.

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