

Diagnosis and management of heat stroke

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QUESTIONS

Before continuing, try to answer the following questions. The answers can be found at the end of the article, together with an explanation. **Please answer True or False:**

1. Regarding heat dissipation and thermoregulation:

- The human body dissipates heat via 4 mechanisms: evaporation, conduction, convection and radiation
- Conductive cooling can be facilitated by increasing the velocity of air flowing over the skin.
- Increasing the gradient of water pressure between skin and environment facilitates evaporative cooling.
- Convection is the body's most effective form of heat loss
- Central control of thermoregulation lies within the medulla

2. Regarding diagnosis of heat stroke:

- A temperature of >40°C is required to make a diagnosis of heat stroke
- Hypotension is a cardinal feature of heat stroke
- Altered mental status is a cardinal feature of heat stroke
- An athlete runs a half marathon on an unusually hot day. After the race they suffer weakness, nausea, vomiting and collapse. This history is consistent with a diagnosis of heat syncope.
- Patients with heat stroke will almost always be tachycardic

3. Regarding risk factors and treatment of heat stroke:

- Dantrolene is an effective treatment for heat stroke
- Diuretics are associated with heat stroke
- Female sex is protective against heat stroke
- Paracetamol is an effective treatment for heat stroke
- Active cooling should stop at 37.5°C

Key Points

- Heat stroke has a mortality rate of between 10-50%.
- Cardinal features are core body temperature of > 40°C and central nervous system dysfunction.
- Patients suffering from heat stroke may have a normal core temperature on arrival at hospital if effective pre-hospital cooling has occurred.
- Mainstays of treatment are rapid cooling and supportive care. Multiple organ support may be required.
- There are many different options for cooling. Choice should depend on local climate, availability and experience.

INTRODUCTION

Despite heat stroke (HS) being originally described over 2000 years ago,¹ the complex pathophysiological processes underlying heat illnesses, including heat stroke, are still not fully understood. Heat stroke is an important condition worldwide with a reported mortality rate of between 10-50%. In addition, 7-20% of survivors are left with persistent neurological damage.^{2,3} Cardinal features of heat stroke are a core body temperature of >40°C and central nervous system dysfunction. This article will outline the different terms used to describe heat related illnesses. The risk factors, prevention, diagnosis and treatment of this important group of illnesses will then be discussed.

HEAT RELATED ILLNESSES

There are a number of different terms used to describe the various heat related illnesses. It has been argued that many of these conditions are not separate entities but rather related conditions within a spectrum.^{2,4-6} Heat stroke is the most severe form of a number of illnesses caused by heat and the failure of normal homeostatic mechanisms. Classical or non-exertional HS (NEHS) refers to heat stroke resulting from high environmental temperature and humidity. Exertional HS (EHS) is secondary to excess heat production during strenuous activity.^{2,3}

HEAT ILLNESS	DEFINITION
Heat cramps	Muscle cramping thought to be secondary to electrolyte deficiencies occurring during exercise
Heat syncope	Fainting due to high ambient temperature causing peripheral vasodilation
Heat exhaustion	Tiredness, weakness, headache, nausea and vomiting are frequent. Significant dehydration may lead to hypotension and collapse. Some authors make a distinction between water-depleted and salt-depleted heat exhaustion. The former occurs more rapidly, especially when associated with exercise. The latter is secondary to lack of dietary electrolyte replacement. Core temperature may not be raised and tissue damage does not occur.
Heat stroke	Core body temperature >40°C due to a failure of the normal thermoregulatory mechanisms. This results in the systemic inflammatory response syndrome and multi-organ failure in which central nervous system dysfunction predominates. Further sub-classified into exertional and non-exertional heat stroke.

Table 1. Definitions of heat related illnesses^{4,5,7}

Normal thermoregulation

Humans are homeostatic organisms. Optimal enzyme function requires body temperature to be maintained within a narrow range around 37°C. Body heat is gained from the environment and from cellular metabolism. Thermoregulation is controlled by the hypothalamus and the autonomic nervous system. Control is achieved via a number of physiological mechanisms. These include alterations of vascular tone (which result in changes in blood flow and blood distribution), shivering and sweating.^{2,4,5} Heat dissipation occurs via 4 processes: evaporation, conduction, convection and radiation.^{2,5} The evaporation of sweat is the most effective method of heat loss; however, as the air temperature approaches body temperature, this mechanism becomes less effective. Absence of sweating is more commonly seen in patients with NEHS in contrast to EHS, where sweating may be persistent.⁴ Conductive heat loss can be greatly increased by immersion in water cooler than body temperature.

In addition to sweating, normal physiological responses to hyperthermia include increases in minute volume, heart rate and stroke volume. Cardiac output may increase 4 fold. Blood is shunted to the peripheries from the core. This may significantly reduce visceral perfusion, particularly intestinal and renal. Comorbidities or medications which reduce an individual's ability to shunt blood peripherally, will increase their susceptibility to HS (see below under Risk Factors).^{2,4}

Pathophysiology

Current thinking is that HS is caused by thermoregulatory failure leading to hyperthermia and systemic inflammatory response syndrome (SIRS). This can result in multi-organ dysfunction, which was previously thought to be as a direct result of tissue injury caused by hyperthermia. Whilst tissue damage by direct thermal injury occurs at temperatures >46°C, metabolism and the inflammatory response is affected at lower temperatures (42-44°C).^{5,8} It now seems likely that the varied effects of HS are due to the combination of both direct thermal injury and SIRS. The sequelae of HS have been noted to be similar to that of SIRS, involving a complex interplay between pyrogenic cytokines, interleukins, endothelial cells, endotoxins, TNF- α and coagulation factors.^{2,3,5,8} A genetic susceptibility to HS has also been suggested, with differences in the expression of genes that encode coagulation proteins, cytokines and heat shock proteins possibly accounting for why some individuals develop HS whilst others do not. A simplified schematic of the pathophysiology of HS is shown in figure 1.

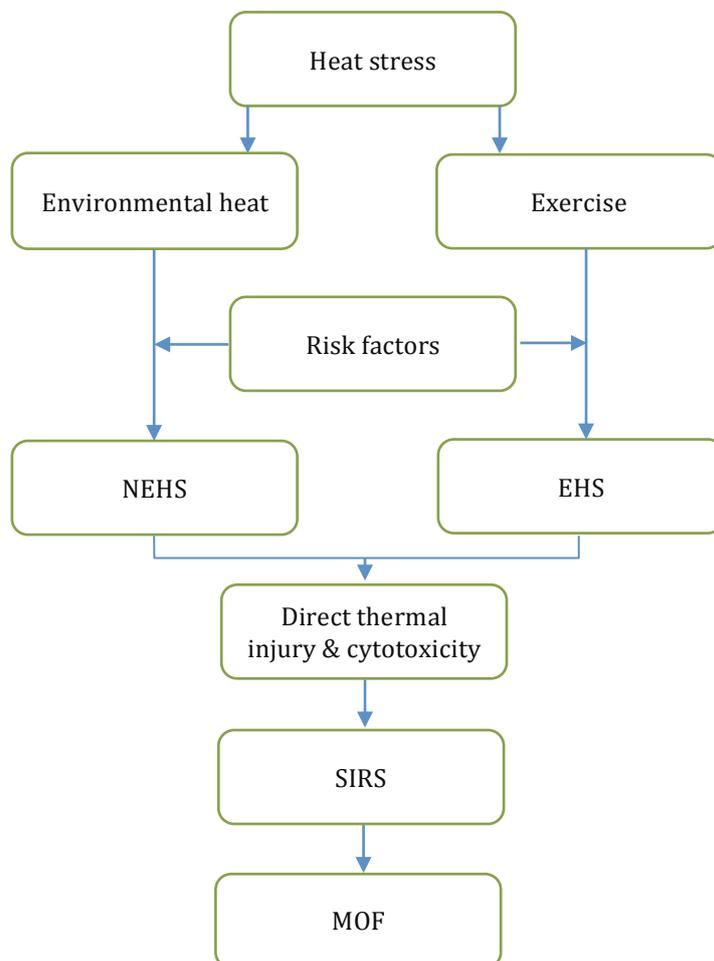


Figure 1. Schematic diagram showing events that lead to heatstroke⁸ NEHS = non exertional heat stroke, EHS = Exertional heat stroke, SIRS = Systemic inflammatory response syndrome, MOF = Multi organ failure.

RISK FACTORS

There are many different risk factors for developing HS (Table 2 and 3). NEHS is commonly seen during heat waves. People at particular risk include those at the extremes of age, the socially isolated and people at large gatherings in hot climates, such as those attending the Hajj, in Saudi Arabia.^{2,4} In contrast, EHS is typically described in healthy people who have been vigorously exercising, including military personnel wearing combat or protective clothing. EHS victims often have not acclimatised to the conditions or the workload.⁵ Environmental factors, physical factors and the different classes of drugs, which predispose to HS are shown in tables 2 and 3 respectively. Sweating can lead to the loss of up to two litres per hour of water together with salt loss. The resulting dehydration and salt depletion have both been shown to further impair thermoregulation.² Female sex seems to be a protective factor for EHS. The reasons for this are unknown. Theories include a protective effect of oestrogens, a lower threshold for triggering thermoregulatory mechanisms or the fact that they produce less heat than their male counterparts due to their smaller muscle bulk.⁴

Environmental risk factors	Physical risk factors
High environmental temperature	Cardiovascular disease
Lack of acclimatisation	Poor cardiorespiratory reserve
Lack of air conditioning	Extreme of ages
Protective clothing	Previous heat stroke
Vigorous exercise	Dehydration (diarrhoea, vomiting)
	Obesity
	Skin disease e.g. anhidrosis, psoriasis, miliaria, scleroderma
	Conditions increasing heat production e.g. thyrotoxicosis
	Concurrent viral illnesses/ Sepsis
	Drug therapy (table 3)

Table 2. Environmental and physical risk factors predisposing to heat stroke^{4,5,7}

CVS drugs	CNS drugs	Drug of abuse	Others
Anticholinergics	Anti-parkinsonian drugs	Amphetamines	Antihistamines
Beta blockers	Benzodiazepines	Cocaine	Laxatives
Calcium channel blockers	Neuroleptics	Ethanol	Thyroxine
Diuretics	Phenothiazines		
	Tricyclic antidepressants		

Table 3. Drug classes predisposing to heat stroke ^{4,5,7} (CVS= cardiovascular system, CNS = central nervous system)

CLINICAL FEATURES

Cardinal features of heat stroke are hyperthermia and central nervous system dysfunction. However, it is important to maintain a high index of suspicion as patients with HS may arrive at hospital with a temperature of <40° if effective pre-hospital cooling has occurred.⁵ HS also affects multiple organ systems which will be discussed below. A history of exposure to hot weather or vigorous activity in the absence of other symptoms may help to make the diagnosis, but important causes such as sepsis, drug reactions and tropical diseases should all be excluded. One other important differential to consider, principally in cases of EHS in hot climate, is hyponatraemia secondary to water intoxication. Rapid onset of hyponatraemia can lead to altered conscious level and seizure, mimicking signs of CNS dysfunction seen in HS. However, this can usually be differentiated from HS by a history of increased fluid intake, a normal pulse rate, normal temperature, polyuria and normotension or hypertension.⁵

Central nervous system (CNS) effects

CNS dysfunction has been attributed to a possible combination of cerebral oedema, cerebral ischaemia and metabolic disturbances.^{4,5} There is a wide range of severity of CNS effects. These include irritability, delirium, encephalopathy and coma. Seizures can occur and are surprisingly more often seen during cooling.^{2,3} Sustained hyperventilation may lead to tetany.^{4,5} The cerebellum is particularly vulnerable to heat stroke and cerebellar atrophy associated with cerebellar dysfunction has been demonstrated on magnetic resonance imaging many months after the initial insult.⁹

Cardiovascular system (CVS) effects

The cardiovascular system is integral to normal thermoregulation and heat dissipation through the redistribution of blood. Redistribution of blood is often compromised in HS and hence the efficacy of this mechanism lost.⁴ Unless there are physiological abnormalities or pharmaceutical factors at play, all patients with HS will be tachycardic. Tachyarrhythmias and hypotension are common. Hypotension is multifactorial in nature. It is often due to a combination of dehydration and peripheral vasodilation, the latter of which is due to increased production of nitric oxide.^{2,4} Hypotension requiring vasopressors is associated with increased mortality and worse neurological outcome.¹⁰ ECG changes are common and have been reported to occur in 85% of HS patients in one series.¹¹ The most frequently observed abnormalities are sinus tachycardia (43-79%) and QT prolongation (61%).^{4,11,12} Both non-specific and specific ST changes associated with coronary artery territories have also been described, as well as conduction defects, such as incomplete and complete right bundle branch block.^{11,12}

Respiratory system effects

Tachypnoea leads to an increased minute volume and arterial blood gas sampling may reflect this. In EHS there is initially a respiratory alkalosis. This may progress to a metabolic acidosis and hyperlactataemia secondary to sustained tissue damage.^{2,4,5} In contrast, patients with NEHS classically present with a respiratory alkalosis alone.² Severe cases of either type of HS can present with pulmonary oedema, pulmonary infarction or acute respiratory distress syndrome requiring sedation, intubation and commencement of mechanical ventilation.^{4,5}

Gastrointestinal effects

Intestinal and hepatic injury can be caused by both direct thermal injury and reduced splanchnic perfusion, the latter being due to preferential shunting of blood to the peripheries. Increased intestinal permeability may allow endotoxins to enter the circulation, thus exacerbating the inflammatory response.^{2,4} Whilst liver function tests are commonly deranged, fulminant liver failure is a rare but very serious complication.

Renal effects

Renal injury in HS is multifactorial. Hypovolaemia, rhabdomyolysis and disseminated intravascular coagulation are all potential contributing factors. Creatinine kinase levels are elevated in both EHS and NEHS although they are higher in the former.⁴ Differing rates for the prevalence of acute kidney injury have been reported, with AKI occurring more frequently in EHS than NEHS.^{4,5}

Metabolic effects

The electrolyte abnormalities that occur in HS have been well described in patients with EHS. It is thought that a similar picture is seen in NEHS.⁴ Hypercalcaemia and hyperalbuminaemia may develop secondary to dehydration.² Hypokalaemia and hypophosphataemia are common early in the course of HS and are thought to be secondary to the combined effects of losses in sweat, the effects of catecholamines and hyperventilation. Hyperkalaemia and uraemia may follow later and renal replacement therapy may be indicated.^{2,4,5} Continued damage to tissue cells causes leakage of phosphate into the extracellular space. Here it may bind to calcium causing hypocalcaemia and hyperphosphataemia.

Haematological effects

Polycythaemia is commonly seen due to dehydration. Cellular metabolism and enzymatic reactions are affected at temperatures between 42-44°C.^{5,8} This includes direct activation platelets leading to microthrombosis. A consumption coagulopathy can occur, which in turn, can lead to excessive bleeding. Presence of a consumption coagulopathy is an indicator of poor prognosis.⁸

PREVENTION

There are many preventative measures that can be taken to minimise the risk of HS. Education and training for those at risk is especially important, as is maintaining hydration and replacing electrolytes lost during hot weather or whilst performing strenuous tasks. Appropriate clothing, equipment and task modification can also help minimise the risk of HS.⁵ Acclimatisation, which describes physiological adaptation to a new environment or climate, also has a role to play. The greatest adaptations are seen within the first 10-14 days, although this may take up to two months. Useful adaptations include increased sweating and expansion of intravascular fluid. The latter helps to reduce the cardiovascular demand and response that is required during periods of raised body temperature.⁵

TREATMENT

In keeping with all medical emergencies, patients with suspected HS should have a rapid assessment of the adequacy of airway, breathing, circulation and neurological status. High flow oxygen should be prescribed and IV access achieved. A rectal temperature should be recorded during the initial assessment if possible.^{4,5,13} The mainstays of treatment after alternative diagnoses have been ruled out is rapid cooling and, where indicated, multi-organ support.² Detailed discussion of multiple organ support is beyond the scope of this article but the same principles apply in the treatment of those with or without heat stroke. Summary of management of heat stroke is shown in Figure 2.

Cooling methods

The aim of cooling is to rapidly dissipate heat from the body's core to the external environment without causing cutaneous vasoconstriction or shivering.² Increasing the gradient of water pressure between the skin and environment facilitates evaporative cooling. Increasing the temperature gradient between these two aids conductive cooling. Cooling via convection may be increased by increasing the velocity of air flowing over the skin.²

It is widely reported that the duration and severity of hyperthermia affects outcome.^{5,13,14} Studies set within urban hospitals have demonstrated that cooling to below 38.9°C within thirty to sixty minutes of arrival at hospital improves survival.^{4,13} Prompt and rapid cooling should therefore commence as soon as HS is suspected. Some experts recommend that active cooling should cease at 39°C to avoid causing hypothermia, however this is dependent on the cooling methods used.⁵

Pre-hospital treatment

Where possible, the patient should cease all activity, be moved into the shade, have any excess clothing removed, be sprayed with water and continuously fanned. Ice packs should be applied externally to the neck, axillae and groins.^{2,13}

Intra-hospital treatment

There is still debate over which method of cooling is most effective.^{2,4,5,13,14} Iced or cold water immersion and evaporative techniques are two of the most widely used methods of cooling.¹³

Ice Water Immersion

Ice water immersion has been shown to be the most effective method for rapid cooling of both EHS and NEHS patients.^{5,10,13} Patient selection is important and this technique may be more appropriate for EHS patients who, in general, are young, healthy and either athletes or military personnel. However, this technique requires specialist equipment that is often not available. Additionally, even when available, there are a number of potential problems. It is often poorly tolerated by the patients, requires a large number of staff and also interferes with the monitoring and resuscitation of the patient.^{4,13} Complications associated with ice water immersion have been found to be more prevalent in elderly NEHS patients.¹⁰ Research has been conducted into the rate of cooling observed with differing water temperatures, ranging from ice water (2°C) to tepid water (20°C). Despite significantly faster cooling being observed with

the use of ice water,¹³ there is still no consensus for the optimal water temperature used in immersive cooling. Our view is that if either ice water is not available or its use is unlikely to be tolerated then cool to tepid water should be used. Placing only the hands and feet of the patient into ice water may be an effective alternative to full body immersion.⁵

Evaporative techniques

Evaporative techniques are less labour intensive. They involve removing the patients clothing and spraying water onto the patient or covering the patient with a soaked gauze sheet and then continually fanning warm air over the skin.¹³ Tepid or warm water should be used to avoid vasoconstriction. Massaging the skin has also been advocated to help overcome this.^{2,13} Whilst evaporative techniques do not have the same efficacy as ice water immersion, they can be started rapidly without the need for specialist equipment, training or large numbers of staff.¹⁴ These techniques also have fewer complications and are better tolerated by patients. A body cooling unit, which uses the principle of evaporative cooling, has been produced but no difference in cooling times was observed when this was compared to covering the patient in a wet sheet and using fans.^{13, 15}

Use of ice packs placed over the large superficial vessels can be easily applied in the pre-hospital environment. Cooling with ice packs alone has been shown to result in longer cooling times when compared to evaporative methods, but when both were applied simultaneously cooling rates increased.^{13,14} The simplicity and safety of ice pack application makes it a favorable choice to use in conjunction with other cooling methods.

Invasive Cooling Methods

Invasive cooling methods, including peritoneal and gastric lavage, have been shown to be effective in a canine model but not more so than evaporative methods.^{13,14} Whilst there have been case reports of the successful use of intravascular cooling for HS,¹⁶ there is a lack of trial evidence to support its use in HS. The risks associated with placing a cooling catheter into a potentially coagulopathic patient must also be considered. Possible benefits of intravascular cooling include rapid and accurate cooling, as well as providing options for invasive monitoring of central venous pressure and a route for central administration of drugs. Correct use will also prevent the development of rebound hypothermia. Infusion of cold intravenous fluids at 4°C has surprisingly not been well recorded in the literature, but this is a simple and effective treatment that should also be considered.

Emergency management of heat stroke	
Prompt and rapid cooling initiated as soon as possible	
Rectal temperature probe monitoring during ABC resuscitation	
Airway + Breathing	<ul style="list-style-type: none"> • Administer 100% oxygen • Assess need for intubation and ventilation
Circulation	<ul style="list-style-type: none"> • Gain IV access, assess fluid balance and begin fluid resuscitation • Assess severity of HS and need for CVC, A-line and inotropic support • Send blood for glucose, FBC, Urea and Electrolytes, LFT, CK, Clotting, ABG • Avoid potassium-containing fluid in patients with hyperkalaemia • Be aware of risk of pulmonary oedema during fluid resuscitation
Disability	<ul style="list-style-type: none"> • Assess conscious level • Check blood glucose and treat hypoglycaemia • Be aware of risk of seizure and treat as needed
Further management	<ul style="list-style-type: none"> • Admit to ICU for severe HS • Stop active cooling at 39°C • Perform urinalysis for myoglobinuria • Consider urine alkalisation and diuresis in rhabdomyolysis • Haemodialysis may be required in ARF with hyperkalaemia • Monitor for hypoglycaemia, liver failure and DIC and treat as needed
Summary of cooling methods for heat stroke	
<ul style="list-style-type: none"> • Ice water immersion produces rapid cooling, however this requires specialist equipment, can be poorly tolerated and can interfere with monitoring and resuscitation • Evaporative techniques are simpler and less labour intensive • Case studies have shown newer techniques such as intravascular cooling devices to be successful • There is no evidence to support the use of pharmacological agents to aid cooling 	

Figure 2. Summary of emergency management and cooling methods for heat stroke

Other Treatments

Despite the implication of pyrogenic cytokines, pharmacological therapies such as paracetamol and non-steroidal anti-inflammatories do not have a role in the management of HS. They have not been found to be beneficial and they should be avoided as they may have adverse effects on renal and hepatic function as well as potentially exacerbating any coagulopathy.^{2,5,14}

Despite dantrolene being successfully used in the treatment of malignant hyperthermia, there is no evidence to support its use in the treatment of HS.^{2,4,13,14,17} However, there is an argument that HS and malignant hyperthermia are part of a broader thermic stress syndrome.¹⁷ A number of patients who have suffered from heat stroke have subsequently tested positive for malignant hyperthermia, and the core temperature of patients with malignant hyperthermia increases more than unaffected individuals when exercising. As it is possible that EHS and malignant hyperthermia are two diseases on a spectrum of altered thermoregulation, testing for malignant hyperthermia is advised after an episode of EHS.⁴ Immunomodulators, including interleukin-1 receptor antagonists, anti-endotoxin antibodies and corticosteroids, have shown some promise in the treatment of heat stroke, demonstrating improved survival in animal models. However, as there have not been any human trials their use cannot be recommended.²

Conclusion

Worldwide, HS continues to be a cause of significant morbidity and mortality. A high index of clinical suspicion is needed in patients with altered mental state and a history of exposure to high environmental temperatures or strenuous activity. Rapid cooling and resuscitative treatments are the mainstays of treatment. Whilst there is currently no consensus on which cooling methods to use, clinical judgement should be used to select appropriate patients for cold water immersion if this is available. Other patients may benefit from a combination of cooling methods, including infusion of cold crystalloids, evaporative cooling and cold irrigation of the stomach and bladder. The possible benefits of intravascular cooling require further research, although when available this is often an effective treatment. At present, there are no pharmacological treatments that have been shown to be effective for HS.

ANSWERS TO QUESTIONS

1. Regarding heat dissipation and thermoregulation:

- a. **True**
- b. **False:** Convective not conductive cooling may be increased by increasing the velocity of air flowing over the skin
- c. **True:** Increasing the gradient of water pressure between skin and environment helps to facilitate evaporative cooling. In practice this can be done by spraying water onto the skin of the patient. In areas of high humidity the water pressure in the air is increased, causing a decrease in evaporation.
- d. **False:** Evaporation of sweat is the most effective method of heat loss.
- e. **False:** Central control of thermoregulation lies within the hypothalamus.

2. Regarding diagnosis of heat stroke:

- a. **False:** Although a temp >40 °C and a suggestive history will help to make a diagnosis of heat stroke, pre-hospital cooling may have occurred. It is unwise to stick rigidly to this criteria.
- b. **False:** Although many patients will be hypotensive, it is not a cardinal feature of heat stroke. However, it is a useful sign that can help differentiate between heat stroke and hyponatraemia (leading to CNS dysfunction) secondary to water intoxication. The latter will be normo- or hypertensive.
- c. **True:** All patients with heat stroke will have an altered mental status which can be wide ranging from mild confusion and irritability to coma.
- d. **False:** Heat syncope is caused by high ambient temperatures causing vasodilatation. Weakness, nausea and vomiting all are symptoms of heat exhaustion. In heat exhaustion, tissue damage does not occur and patient will have a normal core temperature, unlike heat stroke.
- e. **True:** Unless there are physiological abnormalities or concurrent pharmacological treatment (e.g. beta blockers) patients will almost always be tachycardic.

3. Regarding risk factors and treatment of heat stroke:

- a. **False:** Dantrolene has not shown any benefit in patients with heat stroke.
- b. **True:** Diuretics can predispose to dehydration and are a risk factor for heat stroke.
- c. **True:** Female sex is protective against heat stroke. The reasons for this are unclear but current theories include the protective effect of oestrogens, a lower threshold for triggering thermoregulatory mechanisms and a lower muscle mass.
- d. **False:** Paracetamol has not been shown to be effective in aiding cooling, it should be avoided as there is potential for adverse effects on hepatic function.
- e. **False:** Usually active cooling should stop at 39.0 degrees in order to avoid rebound hypothermia. However, newer cooling techniques such as intra-vascular cooling devices allow for greater temperature control and cooling may be discontinued when body temperature reaches 37.0 degrees.

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