Hyperthermia

2

Core Messages

- Hyperthermia is a peripherally (skin and muscle) mediated elevation of body temperature, which greatly differs from fever. Temperature is uncontrolled because the hypothalamic centre is not involved.
- Hyperthermia, in contrast to fever, is uncommon, but it has to be considered in the differential diagnosis of elevated body temperature.
- Although hyperthermia and fever cannot usually be differentiated clinically on the basis of the height of temperature, a temperature above 42 °C suggests hyperthermia. A normal temperature excludes fever but not hyperthermia.
- Hyperthermia has different causes, symptoms and signs than fever. Its management is specific and is also different from that of fever, e.g. antipyretics are ineffective while physical methods are effective.
- Drugs play a major role in causing hyperthermia. In contrast to fever, hyperthermia can largely be prevented.
- Hyperthermia has many causes of which malignant hyperthermia (prototype of increased heat production) and heat stroke (prototype of decreased heat production) are the most common and serious causes.

2.1 Definition

Hyperthermia is a state of thermoregulatory failure resulting from the inability to dissipate heat at a sufficient rate (e.g. heat stroke) or excessive heat production with a normal rate of heat loss (e.g. malignant hyperthermia). Dehydration, the most common cause of hyperthermia, leads to vasoconstriction and decreased sweating, which impair heat dissipation usually causing a mild rise of body temperature. Hyperthermia may coexist with fever: hyperthermia, caused by dehydration, may occur on the top of fever due to infection. In another situation, intense muscular contraction during a febrile seizure (FS)

A. S. El-Radhi (ed.), *Clinical Manual of Fever in Children*,
https://doi.org/10.1007/978-3-319-92336-9_2

Table 2.1 Main differences between fever and hyperthermia

Criteria	Fever	Hyperthermia
Occurrence	Commonest sign	Relatively rare
Clinical findings	Feeling cold, cold skin	Feeling hot, dry flushed skin
Temperature	Usually 38–41 °C	May exceed 42 °C
Principal therapy	Antipyretics	Physical measures
Central regulation	Yes	No
Central set point	Elevated	Normal
Mortality	Unusual	High (excluding minor forms such as dehydration)

may cause hyperthermia, leading to a further increase of fever in FS caused by infection.

In contrast to fever, hyperthermia is not mediated by pyrogen or interleukin-1 (IL-1), and the body temperature is higher than the hypothalamic set point, which is usually normal. Because hyperthermia is not regulated centrally, a temperature in excess of 42 °C is common, and the presence of such degree makes hyperthermia a likely diagnosis. This very high degree of temperature rarely occurs, if ever, with fever alone, even with the most severe infections. Despite this difference, a febrile range of temperature of 38–42 °C does not exclude hyperthermia. Table 2.1 shows the main differences between fever and hyperthermia.

Characteristically, patients with hyperthermia feel warm and attempt to eliminate the heat by stretching out, drinking cold liquid, seeking a cooler environment and removing clothes.

2.2 Physiology

The body temperature is regulated by mechanisms involving the autonomic nervous system (mainly via skin) and the hypothalamus. These are:

- Heat production by muscle activity (increase in muscle tone or shivering) and cellular metabolisms, mainly within the liver, heart and brain through the catabolism of the intracellular proteins, carbohydrates and fats.
- Heat dissipation from the skin and, to lesser extent, the lungs through conduction, convection, radiation and evaporation. The loss is dependent on the humidity and the ambient temperature of the body's surroundings.

Heat production and loss are usually so balanced that a constant body temperature is maintained between 36.6 and 37.9 °C measured rectally.

During the neonatal period, the dominant source of heat production is through non-shivering thermogenesis that increases the metabolic rate without shivering.

This may begin as early as 15 min after birth. The site of non-shivering thermogenesis is brown adipose tissue, which is found predominately in the interscapular area, axillae, perirenal area and around the large vessels in the chest.

When the body is exposed to extreme levels of heat, excessive heat production or impaired heat loss, the thermoregulatory system fails causing heat stress and hyperthermia.

2.3 Effects of Hyperthermia

Not all forms of hyperthermia are dangerous. Hyperthermia is a physiological response to intense exercise, and moderate temperature of 39–40 °C can be found in athletes during hard exercise.

Hyperthermia, particularly when excessive, can induce cellular damage. The brain is especially sensitive to extremes of body temperature. Although it has been difficult to establish a thermal threshold or critical thermal maximum (CTM) in man (defined as the temperature above which tissue damage may occur), a temperature of 42 °C is likely to induce such damage [1]. Complications and mortality above this temperature are related more to the severity of the underlying disease than to the height of the temperature. The upper thermal limit for the survival of most organisms is about 45.0 °C because proteins tend to denature above this temperature. However, it has been difficult to differentiate the clinical effects caused by hyperthermia per se from those caused by related manifestations or complications of hyperthermia, such as hypoxia, hypotension, metabolic acidosis, disseminated intravascular coagulation, azotaemia, hypoglycaemia, circulatory failure or seizures. These secondary disturbances play a part in the pathogenesis of organ damage and in the poor prognosis of hyperthermia. Table 2.2 summarizes the effects of hyperthermia during anaesthesia (see malignant hyperthermia).

Table 2.2 Summary of the effects of hyperthermia during anaesthesia (features are related to hypermetabolic response to anaesthetic agent

• Body temperature: increase of core temperature at a rate of 1–2 °C every 5 min
• Cardiac: tachycardia (earliest sign), decreased output by direct damage of the myocardium causing congestive cardiac failure
• Respiratory: hypoxia, respiratory acidosis
• Renal: failure, acute tubular necrosis, hyperkalaemia, metabolic acidosis
• Gastrointestinal: diarrhoea, liver damage, pancreatitis
• Blood: DIC
• Neurologic: confusion, seizure, cerebral oedema
• Muscular: muscle rigidity, rhabdomyolysis, increased creatinine kinase, myoglobulinaemia, myoglobinuria
• General: widespread vital organ dysfunction

DIC disseminated intravascular coagulopathy

Hyperthermia (e.g. heatstroke) may also cause adverse effects on organs including:

- Renal: Reduction of the glomerular filtration rate when the body temperature increases by 2 °C causing increased concentrations of creatinine and urea.
- Gastrointestinal: Increase of gastrointestinal permeability with loss of the barrier integrity leading to an increase of bacterial toxins.
- Cardiovascular: Hypotension despite hyper-dynamic circulation and increased cardiac output. This is due to blood redistribution and vasodilatation. ECG with high temperature usually shows conduction defects with arrhythmia, QT, ST and T wave abnormalities.
- Cerebral: Initial irritability is soon replaced by lethargy and inactivity, loss of cognitive dysfunction and chronic damage.
- Hepatic: Liver dysfunction with increased enzyme concentrations occur at a temperature of greater than 40.0 °C leading to hepatocellular damage.
- Blood: Coagulopathy is common and contributes to multi-organ dysfunction. Also common are thrombocytopenia, prolonged clotting time, increased plasma fibrin degradation products, spontaneous bleeding and DIC.

2.4 Causes of Hyperthermia

There are several causes of hyperthermia, which are listed in Table 2.3. (The differential diagnosis of the forms of hyperthermia is discussed in Chap. 12).

Table 2.3 Causes of hyperthermia

Hyperthermia caused by increased heat production
• Malignant hyperthermia
• Neuroleptic malignant syndrome
• Serotonin syndrome
• Drug-induced
• Exercise-induced hyperthermia
• Endocrine hyperthermia
• Miscellaneous clinical disorders
Hyperthermia caused by decreased heat loss
• Neonatal hyperthermia
• Dehydration
• Heat stroke
• Haemorrhagic shock and encephalopathy
• Sudden infant death syndrome (SIDS)
• Drug-induced
Unclassified
• Factitious fever
• Induced illness
• Induced illness by proxy

2.4.1 Hyperthermia Caused by Increased Heat Production

Exercise-Induced Hyperthermia

Increase in body temperature and sweating are two normal responses to physical activity. With dehydration (e.g. less than 2% loss of body weight) and hyperthermia, fatigue may occur unless fluid is replaced. This may occur in older children following intense and prolonged exercise, particularly in a hot climate. Maximal exercise produces a nearly 15-fold increase in cutaneous blood flow. The greater surface area to mass ratio in children compared to adults allows greater transfer of heat. For example, an 8-year-old child has a surface area to mass ratio of 360–380 cm^2/kg as compared to 240–260 cm^2/kg in a medium-sized adult [2]. Although the greater surface area produces more sweat, the resulting dehydration may eventually limit heat loss. Children generate more metabolic heat per mass unit than do adults, as evidenced by the higher oxygen uptake seen in children performing the same work as adults. Children have a limited capacity for sweating: secretion per gland in the adult is nearly 2.5 times as high as that in an 8–10-year-old child.

For these reasons, the American Committee on Sport Medicine [3] recommended:

- Caution should be used with prolonged (over 30 min) and intense exercise in environmental temperatures exceeding 30 °C and relative humidity of more than 90%.
- Periodic drinks should be available, e.g. 150 mL of cold tap water every 30 min.
- Clothing should be light, limited to one layer of absorbent material to facilitate evaporation, and sweat-saturated garments should be replaced by dry ones.

Malignant Hyperthermia

Malignant hyperthermia (MH) is an autosomal dominant myopathy causing a hypermetabolic state including massive heat production. Most of the commonly used anaesthetic agents and muscle relaxants can induce MH, but the agents most commonly incriminated are halothane, isoflurane, sevoflurane, desflurane and muscle relaxant succinylcholine. The condition is due to several gene mutations, the commonest being in the skeletal ryanodine receptor gene (PYR1) located on chromosome 19q 13.1. Patients with this gene defect are usually asymptomatic. Some patients have no detectable gene defect. During an acute episode of MH, intracellular calcium increases in skeletal muscle, causing uncontrolled muscle contractions and hyperthermia.

Body temperature during anaesthesia may increase at an alarming rate (1–2 °C every 5 min), reaching a level greater than 44 °C. The hypothalamic thermoregulatory centre functions normally, and therefore antipyretics are ineffective. Normothermia does not exclude MH. Core temperature monitoring should be used instead of skin temperature monitoring for patients at risk of MH.

MH is a potentially fatal condition with a mortality rate ranging between 50 and 70% if untreated. Increased understanding of the condition has led to a decreased

mortality rate to below 5%. The reported incidence ranges from about 1/10.000 to 1/50.000 anaesthetic procedures, with children being at higher risk (1/15000) than adults. Even very young children may be affected.

Risk factors for MH include:

- Genetically susceptible patients who appear normal with an underlying, subclinical muscle disease.
- Susceptibility to heat stress, such as exertional heat stroke.
- Parents of babies who died of SIDS related to high body temperature.
- Patients with chronic myopathy, e.g. central core disease, Duchenne muscular dystrophy, chondrodystrophic myotonia (Schwartz-Jampel syndrome) and those with Noonan syndrome. Interestingly, MH and central core disease have been found to reside near one another on chromosome 19q13.1.
- Some patients with characteristic clinical features, including spinal deformities, ptosis and cryptorchidism.

Clinical features result from the abnormal muscular contractions and are:

- Muscle rigidity, particularly of masseter muscle, causing rhabdomyolysis.
- An increase in end-tidal carbon dioxide, which is often an early sign.
- Tachycardia, rising blood pressure, cardiac arrhythmia, tachypnoea and hyperpnoea (as a result of respiratory and metabolic acidosis).
- A rapid rise in body temperature, reaching a temperature as high as 44.0 °C. When temperature exceeds 41 °C, disseminated intravascular coagulopathy (DIC) is the usual cause of death.

A summary of the effects of MH on the body is shown Table 2.2.

Diagnostic clues include:

- A history of hyperthermia or death among relatives.
- Elevated serum CPK screening.
- In vitro response of the patient's biopsied muscle to halothane (caffeine-halothane contracture test). This gold standard diagnosis is confirmed when both caffeine and halothane test results are positive, while negative results to both caffeine and halothane exclude the diagnosis.
- Deoxyribose nucleic acid (DNA) markers to identify the region on chromosome 19 that carries the gene for MH susceptibility.
- Molecular genetic sampling for MH in the umbilical cord blood [4].

Treatment in established cases during surgery includes:

- Local anaesthesia other than lignocaine should be used whenever possible, e.g. procaine. Also spinal, epidural or regional blocks are recommended. For general anaesthesia, thiopentone (or diazepam) and nitrous oxide are safe.

- Termination of anaesthesia and surgery while continuing ventilation.
- Initiating rapid and aggressive total body cooling with ice packs or ice water, through a nasogastric tube, i.v. and rectally. Antipyretics are ineffective.
- Hundred percent oxygen.
- Correction of acidosis with sodium bicarbonate (1 mg/kg and higher).
- Other medications: i.v. furosemide (1 mg/kg) and mannitol (1 g/kg as 20% solution) to maintain urine output and reduce cerebral oedema; insulin and dextrose to treat hyperkalaemia; hydrocortisone (100 mg 4 hourly).
- Dantrolene, the specific antidote, given in a dose of 2.5 mg/kg and then every 5–10 min. The drug prevents an increase in cytoplasmic calcium. Mortality rate has been reduced to 10% using dantrolene.
- Arrhythmia treatment with lignocaine or procainamide hydrochloride.

Neuroleptic Malignant Syndrome (NMS)

This is a rare but potentially fatal drug-induced syndrome following treatment with dopamine antagonists (neuroleptics such as haloperidol). NMS has the following features:

- Increased extrapyramidal disturbance, altered mental status (particularly delirium), muscle rigidity and hyperthermia.
- An incidence, which varies between 0.02 and 3.2% of patients treated with neuroleptics [5]. Drugs triggering NMS are shown in Table 2.4.
- Cases mostly occur after intake of typical or atypical antipsychotic drugs.
- Certain diagnostic criteria [6] are shown in Table 2.5.
- Symptoms usually subside 5–7 days after discontinuation of the triggering drug. The symptoms may last longer with the use of depot preparations.

Table 2.4 Medications that can induce neuroleptic malignant syndrome

Phenothiazine	Monoamine oxidase inhibitors
Thioridazine	Phenelzine
Chlorpromazine	
Benzodiazepine	Antimanics
Diazepam	Lithium
Butyrophenones	Tricyclic antidepressants
Haloperidol	Imipramine, amitriptyline
Anticonvulsants	Serotonin reuptake inhibitors (SSRIs)
Carbamazepine	Fluoxetine
Phenytoin	
Atypical antipsychotic	Antiemetics
Olanzapine	Metoclopramide
Risperidone	Promethazine
Amisulpride	

Table 2.5 Diagnostic criteria for neuroleptic malignant hyperthermia (modified from reference [6])

Essential	Recent use of antipsychotics, or recent use of other dopaminergic, or recent withdrawal of dopamine agent (e.g. Parkinson's medication carbidopa-levodopa)
Major	Elevated body temperature > 38.0 °C.
	No other cause is found for the temperature
	Muscular rigidity
	Elevated CPK >3 times than normal
Minor	Tachycardia, arrhythmia, dystonia, tremor, tachypnoea, altered consciousness, unstable BP, myoglobinuria

CPK creatinine phosphokinase, *BP* blood pressure

The hyperthermia, often in excess of 41 °C, is partly due to sustained muscle contraction and partly due to central disturbance of dopaminergic pathways within the hypothalamic thermoregulatory centre. NMS is a potentially life-threatening disorder with a reported mortality rate of around 10% of cases [7].

This complication of neuroleptic drugs is to be distinguished from the more common and benign side-effects of these drugs, which may produce fever. Infants with dehydration, fever or coexisting brain damage are at high risk of developing NMS.

Laboratory tests are not diagnostic, but an increased CPK suggests the diagnosis.

Therapy is similar to that of malignant hyperthermia, including stopping medication, rapid cooling measures, close monitoring and the use of dantrolene as a muscle relaxant. Bromocriptine has been used with success. Anticholinergics are of little value.

Serotonin Syndrome (SS)

SS overlaps with NMS. Although clinical features are common to both disorders (elevated body temperature, muscle rigidity, delirium, autonomic instability and high CPK), more typical presentation of SS includes features of:

- Behavioural: confusion and agitation or restlessness.
- Autonomic: tachycardia, hypo- or hypertension, mydriasis.
- Neurologic: myoclonus seizures, clonus, tremor, hyperreflexia.
- Intestinal: diarrhoea.

Hyperthermia in SS is a less consistent finding, compared to malignant hyperthermia and neuroleptics malignant syndrome, and is present in about 50% of cases [8].The syndrome is caused by excessive serotonin stimulation. It has been most commonly associated with an intake of monoamine oxidase inhibitors, tricyclic antidepressants and selective serotonin reuptake inhibitors (SSRIs), such as fluoxetine (Prozac) and sertraline, and the use of cocaine and ecstasy.

Sympathomimetic Syndrome

Sympathomimetics are the most common drugs responsible for hyperthermia. Common symptoms include mental status changes (agitation, confusion, panics, hallucination).They interfere with heat loss and increase heat production through increased muscle activity. Life-threatening hyperthermia caused by these agents is idiosyncratic and not related to duration and mode of administration. The most used drugs are:

- Amphetamine enhances the release of noradrenaline, dopamine and 5-HT from presynaptic nerve terminals and inhibits their reuptake from the synapses.
- Ecstasy (3,4-methylenedioxymethamphetamine = MDMA) is an amphetamine derivative, which causes sympathomimetic activity by releasing serotonin from neurons in the CNS. It was used briefly in the 1970s and 1980s as an adjunct to psychotherapy. Since then, this drug has become popular and abused by teenagers and young adults as an illicit drug, causing a number of adverse events and fatalities. The hyperthermia is mainly attributed to "rave" parties involving high ambient temperatures, excessive dancing and dehydration. In severe cases, particularly with co-use of other illicit drugs, rhabdomyolysis, DIC, seizures, renal and liver failure and cardiac arrest may occur. There is a correlation between the extent of hyperthermia and survival rates in patients taking ecstasy.
- Cocaine stimulates the release of endogenous catecholamines and prevents their reuptake leading to increased metabolism and impairment of heat loss. Intoxication with these two drugs can cause mortality, which is directly related to the degree of the hyperthermia.
- Methylphenidate is a CNS stimulant which is widely used for the management of ADHD in children. Side-effects with the usual daily dose of 10–60 mg include insomnia, irritability, tachycardia and jitteriness. With overdose, symptoms are similar to those of amphetamine overdose, such as agitation, hallucinations, psychosis, tremors, seizures and hyperthermia.
- Baclofen. This drug is used for spasticity and is being increasingly given intrathecally via an implantable pump, where it achieves a high CSF concentration (100 times greater than that achieved by oral route). Its rapid withdrawal (e.g. pump or catheter malfunction) causes a syndrome characterized by altered mental status, tachycardia, hypo- or hypertension, seizures, rebound spasticity (causing muscle rigidity that sometimes progress to fatal rhabdomyolysis) and hyperthermia, which results from increased muscle activity. Baclofen is known to inhibit sympathetic activity at the spinal cord level, and so its withdrawal may cause rebound sympathetic activity. The syndrome may be fatal unless treated promptly by restoration of the drug intrathecally, supportive care and the use of benzodiazepines.

Endocrine Hyperthermia (EH)

Endocrine hyperthermia is a rare endocrine disorder in children compared to adults. Table 2.6 summarizes the main endocrine disorders that may increase body temperature.

Table 2.6 Summary of the main endocrine disorders causing hyperthermia

Disorder	Underlying mechanisms of hyperthermia
Hyperthyroidism	Combination of increased metabolic rate and enhanced sensitivity to amines
Diabetes mellitus	Similar mechanisms to malignant hyperthermia
Pheochromocytoma	Catecholamines causing excessive heat production, peripheral vasoconstriction and IL-6 may be present in the tumour acting as an endogenous pyrogen
Adrenal insufficiency	Dehydration, possibly due to polyuric hypercalciuria
Etiocholanolone fever	Stimulate formation of leukocyte pyrogens

- Hyperthyroidism. About two thirds of all endocrine hyperthermia are due to thyroid diseases [9]. Thyrotoxic crisis and subacute thyroiditis (de Quervain's thyroiditis) may cause a raised body temperature by increasing the metabolic rate and the hypothalamic set point. In contrast to the extreme hyperthermia in thyrotoxic crisis (can reach 41 °C), hyperthermia due to subacute thyroiditis is usually low-grade, often associated with tenderness and pain in the thyroid area, tachycardia and high ESR. It may present with fever alone as a case of PUO. The thyroiditis, which is caused by a viral infection, can be confirmed by abnormal thyroid function tests (high or low T4/T3 levels) with reduced isotope uptake on thyroid scan. Levels of thyroid- stimulating hormone (TSH) are unchanged with increasing body temperature, but T3 levels decrease with high body temperatures.
- Diabetes mellitus. Hyperglycaemic, hyperosmolar non-ketotic syndrome (HHNS) is usually associated with type 2 diabetes mellitus (DM) and is rare in children. Several cases of malignant hyperthermia-like syndrome have been reported in children in association with HHNS in type 1 DM, resulting in rhabdomyolysis and fatality [10]. The underlying aetiology remains unclear (defect in fatty acid oxidation? genetic predisposition?). A rare endocrine abnormality is insulinoma that may be associated with elevation of body temperature and severe hypoglycaemia [11]. A removal of the tumour normalizes the body temperature.
- Hyperparathyroidism is the third most common endocrine disorder after thyroid diseases and diabetes. It is due to increased parathyroid hormone, mostly from parathyroid adenoma, hypercalcaemia (>2.5 mmol/L), bone demineralization and nephrolithiasis. Polyuria may cause hyperthermia. It is one of the rare causes of pyrexia of unknown aetiology.
- Pheochromocytoma with increased catecholamine production may cause excessive heat production as well decreased heat loss subsequent to peripheral vasoconstriction. The presence of a large tumour and tumour necrosis increases the likelihood of hyperthermia that occurs in about a third of patients. Exercise may trigger both sudden hyperthermia and hypertension.

- In adrenal insufficiency, hyperthermia is not common. Elevated temperature may be due to dehydration, related to polyuric hypercalciuria and electrolyte imbalance, autoimmune disorders or tuberculosis.
- Etiocholanolone fever. Etiocholanolone is a major metabolite of testosterone and androstenedione. It acts as a pyrogen causing fever due to the release of interleukin-1 from the leukocytes.

2.4.2 Hyperthermia Caused by Decreased Heat Loss

Neonatal Hyperthermia

A rapid rise in body temperature on the second and third day of life may be due to:

- Dehydration (so-called dehydration fever) is the result of fluid loss, mainly due to evaporation of the amniotic fluid from the baby's body or exposure to a high environmental temperature. This problem results from the infant's greater surface area per unit weight as compared to adults, causing a higher fluid loss through the skin. This condition was identified in 68 out of 358 (19%) febrile neonates, making it the third most common cause of temperature elevation after infection and birth trauma [12]. Hyperthermia should not be confused with fever, which is a response to infection, although both may cause elevated body temperature. Table 2.7 shows the main difference between neonatal hyperthermia and infectious fever. Up to 10% of breast-fed children are said to develop this complication due to insufficient breast secretion and/or infant's reluctance to feed. This incidence can be lowered to about 1% following fluid supplement (through frequent breast feeding to replace fluid loss), which is about the same incidence found in formula-fed babies.

Table 2.7 Differentiating neonatal hyperthermia from infectious fever

Criteria	Hyperthermia	Fever
Incidence	1–10%	1%
Main risk	Dehydration, overheating	Prematurity, PRM[a]
Appearance	Well at initial stage	Unwell
Symptoms	Usually none if hyperthermia is short. If prolonged: tachypnoea, tachycardia, hot and red skin, irritability	Numerous (see Ch 1)
Response of °C to fluid	Rapid normalisation	No change
Leg-rectal temperature[b]	< 1.5 °C	> 3.2 °C
Laboratory findings	Hypernatraemia, high urea	CRP ↑, leucopenia

[a]Premature rupture of membrane
[b]Measurement of the skin temperature of the anterior mid-lower leg simultaneously with rectal temperature or tympanic temperature

- Overheating from mechanical or electrical failure of a warming device or servo-controlled incubators that can cause overheating if the skin sensor becomes detached from the infant or if the baby is left under a radiant warmer for a long period. Overwrapped infants left in a warm room are also at risk.
- Birth trauma may cause a rise in body temperature occurring on the second and third day of life. This phenomenon occurred in 86 out of 358 (24%) infants [12]. Temperature usually subsides within 1–3 days but occasionally persists in the presence of excessive restlessness or convulsions. A probable cause of this hyperthermia is the inability of the sick infant to maintain normal body temperature owing to inadequately developed thermoregulatory mechanisms.

The treatment of hyperthermia in the newborn consists of cooling the infant rapidly by undressing and exposing him or her to room temperature and by frequent breast-feeding. If the skin temperature is higher than 39.0 °C, sponging with tepid water at about 35.0 °C should be initiated until the skin temperature reaches 37.0 °C.

Heat Stroke

Clinical descriptions of 14 different heat-related disorders are recognized in the medical literature (e.g. heat cramps, heat exhaustion, sunburn, etc.), of which heat stroke is the most important heat-related illness and is a medical emergency. It is sometimes called siriasis, based on the biblical reference that occurred coincidentally with the appearance of the Dog Star, Sirius [13]. Heat stroke was described in medicine over 1000 years ago as "another form of fever" by Rhazes (Chap. 13: History of fever). Its recognition in Europe did not occur before the eighteenth century when soldiers were sent to warm countries. Risk factors predisposing to heat-related illness are shown in Table 2.8.

Heat stroke is defined as a core temperature greater than 40.6 °C, accompanied by hot, dry skin and CNS abnormalities such as convulsion, delirium and coma. The two principal causes are high ambient temperature and water deprivation. If the

Table 2.8 Risk factors predisposing to heat-related illness

Age	Environmental
Very young and old	High ambient temperature
	High humidity
	Lack of wind
Dehydration	Drugs
Fever	Lithium, antihistamine, anticholinergic, selective serotonin reuptake inhibitors
Inadequate fluid intake	
Gastroenteritis	
Diuretic use	
Sport (exertional heat stroke)	
Clothing	Condition
Wrapping	Physical or mental disability

temperature rises above 40.2 °C cell deaths occur, and the condition is associated with high mortality of 80%. Heat exhaustion is associated with a core temperature < 40.0 °C.

Heat stroke is due to failure of the heat-regulating mechanisms of the hypothalamus subsequent to inhibition of sweating. Cytokines in the CNS leads to increased intracranial pressure, thus reducing the blood flow and causing neural injury. Initially, there may be sweat loss leading to dehydration, which aggravates the hyperthermia.

Heat stroke has been reported from a number of geographical areas including:

- In the USA [14] and Italy [15], infants who were left sleeping in a parked automobile under the sun with inadequate ventilation may suffer heat stroke. In 2003, the number of children reported who died from heat stroke after being left unattended in motor vehicles was 42.
- In the UK and other European countries where excessive wrapping is sometimes practiced in infants (mainly from lower socioeconomic classes). This swaddling, which in an ancient practice, has become increasingly popular as a sleep-promoting intervention, sometimes resulting in fatalities [16].
- In Melbourne, Australia, heat stroke occurred during a recent heat wave.
- In the tropics, heat stroke may occur in children as a result of combined salt and water deprivation or severe sunburn.

The cardinal features of heat stroke include:

- Body temperature: > 40.6 °C.
- Skin: hot, dry and red (sweating may or may not be present).
- CNS abnormalities: alteration of consciousness, dizziness, headache, convulsion and coma, uncontrollable muscle twitching.
- Cardiac: Tachycardia, arrhythmia and failure as a result of extensive haemorrhage in the myocardium.
- Gastrointestinal: diarrhoea, nausea, vomiting, cramps, jaundice (liver failure).

In addition, children are usually in shock (due to maldistribution of the blood to the circulation), with metabolic acidosis. Clinical evaluation may confirm the presence of renal failure, DIC, rhabdomyolysis (due to severe muscular contraction), hepatic enlargement with elevation of the enzymes and anaemia due to increased RBC destruction, thrombocytopenia and hyperkalaemia, with characteristic ECG abnormalities.

A child with heat stroke should:

- Be referred to an intensive care unit with facilities for continuous monitoring and ventilation. The two main goals of therapy are cooling and support of circulation.
- Undergo rapid cooling, best achieved by removing the clothes, sponging with ice water (or better immersing into ice water) until body temperature reaches

38.5 °C. Then the patient is moved to a bed and wrapped in a blanket. In severe or resistant cases iced-intravenous solution, iced-saline gastric lavage and cold saline enema may be needed.
- Be vigorously massaged to promote vasodilatation and fanning to increase convection. Continuous oxygen therapy is usually given routinely.
- Have IV fluid therapy aimed at correction of dehydration and balancing electrolytes. Plasma expanders and mannitol (1 g/kg of 20% solution, infused over 15–20 min) are required to treat cerebral oedema and renal under-perfusion.
- Be treated for hyperkalaemia with glucose and insulin. Renal failure may require early dialysis, along with adequate fluid, electrolytes and bicarbonate.

Despite intensive treatment, the prognosis of heat stroke is poor, with a mortality ranging from 17 to 70%, depending on severity of the heat stroke and age of the patient. Post-mortem examination reveals cerebral oedema and haemorrhage in various organs.

Haemorrhagic Shock and Encephalopathy (HSE)

This form of hyperthermia was described by Levin et al. in 1983 [17].Despite extensive investigations, including viral and bacteriological studies, no specific cause has been found. Although clinical features are similar to heat stroke, the majority of reported cases had no evidence of wrapping, fluid deprivation or high environmental temperature. It was later suggested that HSE may be a manifestation of a genetic defect in the production or release of serum protease inhibitor alpha-1-trypsin [18].

The median age of affected children is 5 months (range 17 days to 15 years), and nearly 90% have been less than 1 year of age. Usually, the children have been completely well with only mild non-specific symptoms, such as an upper respiratory tract infection or febrile gastroenteritis, 2–5 days prior to the onset of HSE. Then abruptly they develop:

- Severe shock, manifested clinically by collapse, pallor, cyanosis and mottled skin. Hypotension is a late sign of shock.
- Encephalopathy manifested with sudden onset of seizures and coma.
- Hyperthermia a constant finding, with a temperature usually above 41 °C.
- Bleeding due to DIC, with diarrhoea, may be striking, resulting in severe anaemia requiring transfusion.

Examination reveals hepatomegaly and acidosis with shallow respirations. During the next few hours, renal failure becomes established with increased creatinine, hyperkalaemia and acidosis. Additional laboratory abnormalities include leukocytosis, hypernatraemia, elevated serum levels of creatinine phosphokinase (CPK), liver enzymes and trypsin, hypoglycaemia and hypocalcaemia, thrombocytopenia, reduced factors II, V, hyperfibrinogaemia and alpha-1-antitrypsin.

Haemorrhagic shock and encephalopathy must be differentiated from:

- Heat stroke with its history of fluid deprivation and high ambient temperature.
- Septicaemia with its less abrupt presentation.

- Reye's syndrome with its elevated plasma ammonia and characteristic histological findings of the liver; possible aspirin intake.
- Haemolytic uremic syndrome with its haemolysis, pronounced anaemia.
- Toxic shock syndrome and Kawasaki disease (both have a less dramatic onset) and accidental intake of toxin.

There is no specific treatment for HSE, and management is similar to that discussed for malignant hyperthermia and heat stroke. Prognosis is poor with a mortality of 80% and severe neurological squeal in the majority of surviving cases. CT scan and autopsy show focal haemorrhage in many organs and cerebral oedema.

Drug-Induced Hyperthermia

- Anticholinergic poisoning. The dominant clinical features are:
  Central: confusion, agitation, hallucination and seizures
  Peripheral: dry mucous membranes, thirst, flushed face, blurred vision, dilated pupils and hyperthermia

  The hyperthermia is mainly caused by decreased sweating.
  Drugs with anticholinergic activity include

Antispasmodic	For example, belladonna, propantheline
Antiemetic	For example, hyoscine, cyclizine, promethazine
Atypical antipsychotics	For example, olanzapine
Bronchodilator	For example, ipratroprium
Antihistamine	For example, chlorpheniramine
Antidepressant	For example, amitriptyline, imipramine

Hyoscyamine is one of the principal alkaloid components of belladonna. Hyoscyamine sulphate drops are sometimes prescribed for infantile colic. Herbal tea and Chinese herbal medicine have also caused anticholinergic poisoning and hyperthermia.

Treatment includes rapid and aggressive cooling. The specific antidote is physostigmine. Benzodiazepines are also effective.

Other hyperthermia-induced drugs include:

- Topiramate is an anticonvulsant drug with a beneficial effect on various seizure disorders. Side-effects include hypohidrosis (or anhidrosis) causing hyperthermia, which is manifested as prolonged or intermittent elevated body temperature. The decreased production of sweat can be confirmed by pilocarpine iontophoresis sweat test.
- In a study of 277 children on topiramate, 161 (58%) developed adverse events, including nervousness, weight loss and hyperthermia [19]. These side-effects disappeared in most cases after reducing the dose. They are rare on monotherapy. The hyperthermia is probably due to inhibition of carbonic anhydrase in human eccrine sweat glands.
- Salicylate poisoning: see Chap. 10, Management of fever

2.4.3 Unclassified Hyperthermia

Sudden Infant Death Syndrome (SIDS)

This important subject is included because of its possible link to hyperthermia.

The accepted definition of SIDS is:

- An infant's sudden and unexpected death, which remains unexplained after thorough post-mortem examination.
- A thorough investigation of the death scene fails to find the cause of SIDS.
- A diagnosis of exclusion. Symptoms such as upper respiratory tract infection with possible fever, which do not have serious effects on the child's condition, do not exclude the diagnosis.

Although SIDS is still the leading cause of death in infants one to 12 months of age, its rate has declined since the start of the "Back to Sleep" campaign in 1991 (UK) and 1992 (USA).

- In the USA, the rate in 1992 was 1.2 death per 1000 live births, which decreased to 0.56 death per 1000 live births (a reduction of 53%) over 10 years [20]. During this period, the prevalence of prone positioning has decreased from 70 to 11.3%.
- In the UK, there has been a remarkable fall in incidence to 0.4 death per 1000 live births in the year 2000 and a further fall to 0.26 in the year 2003 [21].

Despite extensive research over the past decades, the cause of SIDS is unknown. The predominant hypothesis is that certain infants have maldevelopment or delayed maturation of the brainstem neural network, which is thought to be involved with arousal, chemosensitivity, respiratory drive, thermoregulation and blood pressure response. Long QT interval may also cause SIDS. A multifactorial cause, rather than a single one, appears likely. Risk factors associated with SIDS are shown in the

Table 2.9 Risk factors that contribute to SIDS

General factors	Hyperthermic factors
Maternal smoking	Prone position
Low birth weight	Bed-sharing with parents
IUGR	Overwrapping, bundling
Twins	High environmental temperature
Opiate addiction	Respiratory infections
Young maternal age	
Maternal alcohol consumption	
Deprived socio-economic status	
Polystyrene-filled cushions	
Sibling with a history of SIDS	
Prolonged QT-interval in the ECG	

Table 2.9. The risk peaks at 2–4 months of age and is low during the neonatal period (only about 4% of all SIDS cases). The two important factors are prone position and maternal smoking.

Although the vast majority of infants who sleep prone are not in danger of SIDS, up to 88% of SIDS victims were found in this position. A child in prone position may have limited head movement and thus limited access to fresh air. This factor may also explain the low incidence of SIDS in Asian children, who usually sleep in a supine position.

SIDS and Hyperthermia. Hyperthermia (e.g. in the form of heat stroke) has been implicated as a cause of SIDS. It may cause apnoea as a result of transient loss of respiratory chemoreceptor sensitivity. The most convincing evidence of the relationship between SIDS and hyperthermia was reported by Stanton [22], who found that 32 of 34 cases (94%) of SIDS victims were excessively clothed in an unusually warm environment or were hot and sweaty when found dead. In these cases, sweat and high rectal temperature suggested the presence of hyperthermia.

The mechanisms leading to hyperthermia in SIDS include:

- Excessive wrapping, thick bedding, high environmental temperature (such as proximity to a heat source) and a prone position, which may further limit heat loss through the face in the presence of overwrapping. Side sleeping is not as safe as supine sleeping
- Mild infection, commonly preceding SIDS, may produce fever, which in combination with excessive wrapping could produce heat stroke and SIDS.
- Bed-sharing infants experience warmer thermal environment than those sleeping in a cot.
- In addition, a period of thermoregulatory imbalance may exist during infancy where heat production in relation to surface area reaches a maximum by about 5 months of age, while dissipation of heat by sweating develops more slowly over the first year of life.

Factitious Hyperthermia (FF)

The creation of "fever" by manipulation (usually thermometer manipulation) is rare in children, particularly below the adolescent age. However, factitious hyperthermia is occasionally encountered in the differential diagnosis of PUO, occurring in about 2% of a large study of mainly adult cases [23]. It can be the most difficult diagnosis to establish. For example, an adolescent of 15 years of age from the USA with an 8-month history of fever was described [24]. It is true to say that the question as to whether a patient actually has a fever or not is rarely raised.

Many patients with FF appear to seek attention and feel protected in a hospital environment. Occasionally, it is an escape from intolerable conditions at home. Methods commonly used by these patients to induce FF include holding the thermometer next to a hot-water bottle, rubbing it against bedclothes, rinsing the mouth with a hot liquid before inserting a thermometer or switching thermometers.

Diagnostic clues include:

- Discrepancy between the generally well appearance of the child and the recorded "fever".
- The absence of warm skin, sweating, tachycardia and the usual diurnal variation of the fever.
- Normal laboratory findings, e.g. inflammatory markers: leukocytes, CRP.
- Normal body temperature when a nurse attends the temperature recording.

Induced Illness (Factitious Illness, Munchausen Syndrome)

This is the most extreme form of factitious disorder. In 1951, Asher described patients who fabricated illnesses and subjected themselves to medical investigations and treatment, including operation [25].Although principally an adult disease, the syndrome has also been reported in children [26] and is characterized by features shown in the Table 2.10.

In a review of literature over 30 years [27], 42 children (mean age 13.9 years) with falsified illness were identified. The most commonly falsified conditions were fevers (13%). The deception was carried out by warming thermometers with heating pads.

Induced Illness by Proxy (Factitious Illness by Proxy)

In 1977, Meadow reported two children whose parents by fabrication caused them to undergo innumerable, harmful medical procedures [28]. In a second report in 1982 [29], Meadow presented 19 children under the age of 7 years (above this age children are likely to reveal the deception) of which four had fever as the fabricated sign (incidence of fever generally is around 10%). Meadow considered epilepsy to be the most frequently fabricated illness. Mortality rate among children diagnosed is 9%.

The syndrome involves a parent (usually mother) or caregiver who tends to be young and articulate and who fabricates an illness in a child. The motivation for the perpetrator's behaviour is a psychological need to have the child assuming the sick role. The perpetrator often has a personality disorder and a significant family

Table 2.10 Main features of induced illness

Essential features
Pathologic lying
Simulation of a disease
Wondering
Minor features
Unusual or dramatic history
Previous treatment in hospital
Previous diagnostic procedures
Multiple scars
Experience in a medical field
Antisocial personality trait

dysfunction. Family history of unexplained child's death may be elicited. The syndrome is characterized by:

- Discrepancy between history, clinical findings and the child's healthy appearance.
- Mother appears less worried about the child's illness than medical staff. She usually welcomes even painful tests and procedures for her child.
- The child's "illness" is recurrent and cannot be explained medically.
- There is a history of multiple medical procedures.
- Symptoms and signs disappear in the mother's absence.
- Mother usually attentive and present in hospital.
- Once confronted, the perpetrator typically denies any knowledge.

Clinical presentations generally follow two patterns:

- Apnoea, feeding problems, seizures and cyanosis (seen during infancy).
- Diarrhoea, vomiting and fevers (seen in older children).

Although the majority of fabricated illnesses are not life-threatening, recurrent episodes of cardiorespiratory arrest induced by a mother have been reported, suggesting that Munchausen syndrome by proxy is a form of child abuse. A report of 56 children supported this view: a substantial proportion of the victims sustained failure to thrive, nonaccidental injury, inappropriate medication or neglect [30].

2.4.4 Therapeutic Effects of Hyperthermia

It has been known for thousands of years that hyperthermia helps the body against some diseases. In 1970s and 1980s, several trials have shown that hyperthermia combined with radiation or chemotherapy produced better anticancer treatment over radiation and chemotherapy alone. Therapeutic application of hyperthermia and the means to produce it are shown in the Table 2.11. Its potential use includes:

Table 2.11 Therapeutic application of hyperthermia (or fever) and means of producing it

Application of heat:	Local
	Deep (<3 cm under the skin)
	Superficial
	Regional
	Deep (<3 cm under the skin)
	Superficial
	Whole body
Externally produced heat	Microwave, thermal blanket, lasers, heating rods, infrared radiation, high frequency electrotherapy, ultrasound, extracorporeal
Internally produced heat	Pyrogens (bacterial substance producing fever; fever therapy)

Infectious diseases

Hyperthermia stimulates the immune system, including production of interferon (INF). Examples of diseases treated by hyperthermia are:

- During the nineteenth century, medical professionals observed that tumours regressed in size after an episode of a high fever due to infection. Wagner von Jauregg in 1917 treated neurosyphilis with malarial fever, for which he won the Nobel Prize (see Chap. 13). The best results of fever therapy were observed in gonorrhoea and syphilis, including their complications, such as arthritis, keratitis and orchitis. Approximately 70–80% of the cases treated were arrested using artificial hyperthermia or malarial fever in the range of 40.5–41.0 °C for about 50 h administered in several sessions. *Borrelia* spirochaetes, the cause of Lyme disease, might also be susceptible to hyperthermia greater than 41 °C.
- Viral nasopharyngitis: Nasal insufflations of humidified air at 43 °C showed suppression of symptoms in 78% of patients [31].
- Human immunodeficiency virus (HIV) infection: Temperatures of ≥42 °C maintained for ≥25 min have been shown to inactivate approximately 25% of the HIV [32]. A daily use of such temperatures lowers the population of actively infected cells by 40%. A reduction of the virus by 40% would effectively reverse the depletion of T cells. HIV-infected cells are more sensitive to heat than healthy lymphocytes. This susceptibility increases when the cells are pretreated with tumour necrosis factor.

Musculoskeletal disorders

Local and regional hyperthermia have been used since ancient times to treat musculoskeletal disorders. Tissue heated at 44 °C increases extensibility of the tissue, decreases joint stiffness and muscle spasms. These effects occur mainly through increased blood flow. Whole body hyperthermia also induces soluble tumour necrosis factor receptors (TNF-R), which is an anti-inflammatory product.

Cancer

Hyperthermia is regarded as the fifth treatment of cancer after surgery, chemotherapy, radiotherapy and immunotherapy. Therapeutic hyperthermia as an adjunctive therapy has been used since 1970s to treat patients with cancer, yielding some positive results with complete or partial remission of the tumours. Hyperthermia has been shown to synergistically enhance the radiation response and cytotoxicity of chemotherapy. Heating can be achieved using microwaves, radio waves, laser and ultrasound waves. There is evidence that hyperthermia of 42 °C or greater for 30–60 min is tumouricidal. This effect of cell death is mainly caused by protein denaturation at hyperthermic range of 40–44 °C. Hyperthermia also causes cellular damage including apoptosis leading to cell death.

Hyperthermia in combination with chemotherapy has been shown to be effective in:

- Some patients with advanced malignancies, e.g. renal cell carcinoma [33].
- The management of retinoblastoma, which has gradually changed over the past 10–15 years: enucleation is preferable only for a large tumour that fills most of

the globe [34]. Over 95% of children with retinoblastoma are cured with modern techniques. These include the use of transpupillary thermotherapy alone or in combination with systemic chemotherapy (chemothermotherapy).
- Using regional hyperthermia (RHT) chiefly in children with sarcoma or germ cell tumours located in the abdomen, pelvic region, chest wall and extremities to improve operability [35].
- Treating malignant brain tumour such as glioblastoma [36] and malignant melanoma.

References

Clinical Effects of Hyperthermia

1. Bynum GD, Pandolf KB, Schuette WH, et al. Induced hyperthermia in sedated humans and the concept of critical thermal maximum. Am J Phys. 1978;235:R228–36.

Exercise-Induced Hyperthermia

2. Bar-Or O. Climate and the exercising child-review. Int J Sports Med. 1980;1:53–65.
3. Committee on sports medicine. Climatic heat stress and the exercising child. Pediatrics. 1982;69:808–9.

Malignant Hyperthermia (MH)

4. Girard T, Joehr M, Schaefer C, et al. Perinatal diagnosis of malignant hyperthermia susceptibility. Anesthesiology. 2006;104:1353–6.

Neuroleptic Malignant Syndrome (NMS)

5. Caroff SN, Mann SC. Neuroleptic malignant syndrome. Med Clin North Am. 1993;77:185–202.
6. Nierenberg D, Disch M, Manheimer E, et al. Facilitating prompt diagnosis and treatment of the neuroleptic malignant syndrome. Clin Pharmacol Ther. 1991;50:580–6.
7. Oruch R, Pryme IF, Engelsen BA, et al. Neuroleptic malignant syndrome: an easily overlooked neurologic emergency. Neuropsychiatr Dis Treat. 2017;13:161–75.

Serotonin Syndrome

8. Halloran L, Bernard DW. Management of drug-induced hyperthermia. Curr Opin Pedaitr. 2004;16:211–5.

Endocrine Hyperthermia

9. Simon HB, Daniels GH. Hormonal hyperthermia, endocrinological causes of fever. Am J Med. 1979;66:257–63.
10. Kilbane BJ, Mehta S, Backeljauw PF, et al. Approach to management of malignant hyperthermia-like syndrome in pediatric diabetes mellitus. Pediatr Crit Care Med. 2006;7:169–73.
11. Goodman EL, Knochel JP. Endocrine hyperthermia. Heat stroke and other forms of hyperthermia. In: Mackowiak P, editor. Fever: basic mechanisms and management. New York: Raven Press; 1991. p. 281.

Neonatal Hyperthermia

12. Ws C. The early detection of pyrexia in the newborn. Arch Dis Child. 1963;38:29–39.

Heat Stroke

13. Knochel JP. Environmental heat loss. Arch Intern Med. 1974;133:841–65.
14. McLaren C, Null J, Quinn J. Heat stroke from enclosed vehicles: moderate ambient temperatures cause significant temperature rise in enclosed vehicles. Pediatrics. 2005;116:217.
15. Ferrara P, Vena F, Caporale O, et al. Children left unattended in parked vehicles: a focus on recent Italian cases and a review of literature. Ital J Pediatr. 2013;39:71.
16. Van Gestel JPJ, L'Hoir MP, ten-Berge M, et al. Risk of ancient parties in modern times. Pediatrics. 2002;110(6):1–3.

Hemorrhagic Shock and Encephalopathy (HSE)

17. Levin M, Kay JDS, Gould JD, et al. Hemorrhagic shock and encephalopathy. A new syndrome with high mortality in young children. Lancet. 1983;2:64–7.
18. Levin M, Pincott JR, Hjelm M, et al. Haemorrhagic shock and encephalopathy: clinical, pathologic, and biochemical features. J Pediatr. 1989;114:194–203.

Drug-Induced Hyperthermia

19. Grosso S, Franzoni E, Iannetti P, et al. Efficacy and safety of topiramate in refractory epilepsy. J Child Neurol. 2005;20:893–7.

Unclassified Hyperthermia

Sudden Death Infant Syndrome (SIDS)

20. American Academy of Pediatrics. The changing concept of SIDS: diagnosis, coding shifts, controversies regarding the sleeping environment. New variables to consider in reducing risk. Pediatrics. 2005;116:1245–55.

21. Blair PS, Sidebotham P, Berry PJ, et al. Major epidemiological changes in SIDS: a 20-year population-based study in the UK. Lancet. 2006;367:314–9.
22. Stanton AN. Overheating and cot death. Lancet. 1984;3:1199–201.

Factitious Hyperthermia

23. Rumans LW, Vosti KL. Factitious and fraudulent fever. Am J Med. 1978;65:745–55.
24. Edwards MS, Butler KM. Hyperthermia of trickery in an adolescent. Pediatr Infect Dis J. 1987;6:411–4.

Induced Illness

25. Asher R. Munchausen's syndrome. Lancet 1951; 1: 339–41.
26. Sneed RC, Bell RF. The dauphin of Munchausen: factitious passage of renal stones in a child. Pediatrics. 1976;58:127–30.
27. Libow JA. Child and adolescent illness falsification. Pediatrics. 2000;105:336–42.

Induced Illness by Proxy

28. Meadow R. Munchausen syndrome by proxy: the hinterland of child abuse. Lancet. 1977;2:343–5.
29. Meadow R. Munchausen syndrome by proxy. Arch Dis Child. 1982;57:92–8.
30. Bools CN, Neale BA, Meadow SR. Co-morbidity associated with fabricated illness (Munchausen syndrome by proxy). Arch Dis Child. 1992;67:77–9.

Therapeutic Effects of Hyperthermia

31. Yerurshalmi A, Lwoff A. Traitement du coryza infectieux et des rhinitis persistantes allergiques par la thermotherapy. Camp Rendus Seances Acad Sci (Paris). 1980;291(Ser D):957–9.
32. Pennypacker C, Perelson AS, Nys N. Localized or systemic in vivo heat inactivation of HIV: a mathematical analysis. J Acquir Immune Defic Syndr Hum Retrovirol. 1995;8:321–9.
33. Ismail ZRS, Zhavrid EA, Potapnev MP. Whole body hyperthermia in adjuvant therapy of children with renal cell carcinoma. Pediatr Blood Cancer. 2005;44:679–81.
34. Shields CL, Meadows AT, Leahey AM, et al. Continuing challenges in the management of retinoblastoma with chemotherapy. Retina. 2004;24:849–62.
35. Seifert G, Budach V, Keilholz U, et al. Regional hyperthermia combined with chemotherapy in paediatric, adolescents, and young adult patients: current and future perspectives. Radiat Oncol. 2016;11:65.
36. Man J, Shoemake J, Ma T, et al. Hyperthermia sensitizes glioma stem-like cells to radiation by inhibiting AKT signaling. Cancer Res. 2015;75(8):1760–9.