Disorders of thermoregulation

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Healthy humans are homeothermic

Body temperature (BT) is maintained within a narrow range, despite changes in environmental conditions, physical activity and other influencing factors.

**Core temperature:** Normal core temperature: 36.1-37.0 °C
The depths of the body cavities have a truly constant temperature ~ due to a balance between heat production/uptake and heat loss.

**Surface temperature** of the skin and extremities can vary over several °C.

BT measurement
- Orally (0.3 to 0.5°C higher than the surface temperature)
- Rectally (0.5 to 1°C higher than the surface temperature)
- Reliable axillary measurement (in the closed arm-pit) takes up to 30 min
- Tympanic membrane (TM) thermometer
  Measures radiant heat energy from the TM and nearby ear canal
  A quick method (2-5 s), but the values are more variable.
Factors influencing BT

- Diurnal variation of BT± 0.5 °C
  - min. at ~ 3 a.m.
  - max. between 5 p.m. and 10 p.m.
- Physical activity
- Behavioral, emotional impulses
- Metabolic changes, nutrition
- Age:
  - Newborns, infants transient elevations in temperature) or cooling can occur very easily (the surface/volume ratio is very high)
  - Elderly people with heart failure or those taking diuretics have incr. risk for thermoregulatory failure due to decreased cardiac output
- Hormonal changes
  - Thyroid hormones
  - During the 2nd half of the menstrual cycle: BT rises by 0.5 °C
  - Pregnancy
  - Menopause: hormonal changes (↓estrogen, ↑LHRH, FSH, LH) the hypothalamic set point is lower than normal → hot flashes at normal BT and transient activation of thermolysis
Control of BT

- Primary thermoregulatory control center: in the preoptic and posterior regions of hypothalamus
- Behavioral thermoregulatory control: like choice of appropriate dress, seeking shade in summer are the most effective thermoregulatory responses
- Autonomic thermoregulatory control
  - Skin surface, deep abdominal and thoracic tissue, spinal cord, hypothalamus and other parts of the brain (each contributes approximately 20%)
In a cold environment

- Cold receptors in the skin (A delta fibers) cutaneous vasoconstriction, voluntary muscle activity and shivering, increased metabolic rate, increased heat production, decreased thermolysis

- Non-shivering thermogenesis: in newborns and infants is mediated by β₃ adrenergic receptors on nerves found in brown fat (back and shoulders)

In a warm environment (during heavy exercise or at high surrounding temperature)

- Stimulation of central and peripheral warm receptors (C fibers) activated, heat loss due to incr. internal heat flow (from the inner organs to the skin)

- The countercurrent heat exchange between adjacent arteries and veins decreases, leading to increased capillary blood flow, sweating and heat dissipation
  - Venous return diverted to the superficial veins in the skin, more heat is carried to the periphery

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Heat production (thermogenesis)
- Is a function of energy metabolism, (e.g. thyroid thermogenesis, catecholamines, glucocorticoids) and GI production of heat during digestion
- At rest ~56% of the basal heat is generated by the internal organs and 18% by musculature and skin (brain 16%; other sources: 1 %)
- During exertion the muscle work can account for up to 90% of the heat produced

Heat uptake: by radiation, conduction and convection
- When the surrounding temperature exceeds the $t^\circ$ of the skin heat
  - Input to a body from the sun or from a heat lamp
Heat loss (external heat flow)

1. Radiation
   Heat transfer between the body and nearby human beings or objects with lower temperature
   As long as air temperature is less than body temperature, 65% of the body's heat is lost by radiation

2. Conduction
   Is the transfer of heat to the surrounding, cooler environment via direct physical contact
   It accounts for 2% of the body’s heat lost

3. Convection
   When the surrounding air is warmed up by the skin, is replaced by a cooler layer
   Convection and conduction are enhanced by a breeze or by a cooler fluid medium
   Is influenced by the blood circulation of the skin
   It accounts for 10% of the body's heat loss

4. Evaporation of water
   During heavy exertion or at high surrounding temperature (>36 °C) heat dissipation occurs enterily by evaporation
   Influenced by: blood circulation, humidity and temperature of the air, wind
   When the humidity of the air (e.g. tropical rainforest) increases, heat loss through sweating decreases considerably or cease completely
   **Perspiratio insensibilis**: through the skin and the airways ~ 1 l/day
   **Perspiratio sensibilis**: via the activated sweat glands ~ 10 l/day
• Thermal comfort (indifferent temperature)
  ○ Neither activation of sweat glands nor shivering is necessary for maintaining the core temperature constant
  ○ Depends on environmental temperature, clothing, muscular work, wind, air, humidity and radiation

• Acclimatization to high temperature may take 4 to 7 days
  ○ Sweat secretion increased, salt content of sweat decreased, thirst and water intake increased, ADH, aldosterone secretion increased (potassium loss), renal blood flow (RBF) decreased, respiratory and pulse rates increased.
Endogenous heat disorders due to set-point changes

Low-grade fever
- BT rises but does not exceed the value of 37.5 °C
- Habitual hyperthermia: psychogenic fever in young females
- Hyperthyroidism
- Rheumatic fever
- Tuberculosis
- Neoplastic diseases
- Elderly: may have modest fever, even in severe infections

Fever
- Definition of fever: a.m. body temperature of greater than 37.2 °C or a p.m. temperature of greater than 37.7 °C orally or simply as an elevation of body temperature above the normal daily variation
- Moderate fever: 38.0-39.0 °C
- High grade fever: 39.1-40.0 °C
- Hyperpyrexia: fever > 40.5 °C (often due to CNS hemorrhage)
• Causes of fever
  ○ Acute and chronic infections: bacteria, viruses, fungi, protozoa
  ○ Mechanical trauma causes tissue destruction
  ○ Tumors: carcinoma of the pancreas, lung or bone, acute leukemias, lymphomas
  ○ Hematopoietic disorders: e.g. acute hemolytic episodes
  ○ Vascular accidents (AMI, stroke), autoimmune diseases, metabolic disorders (e.g. thyroid crisis)
  ○ Drugs: sulfonamides, iodides, barbiturates, laxatives
    ■ Careful history of drug intake in unexplained fever cases
Mechanism of fever

- Exogenous pyrogens: bacteria (spirochetes, endotoxins, exotoxins), viruses, immune reactions, hormones (e.g. progesterone), drugs, trauma → induce the release of endogenous pyrogens (IL-1,6,8; IFN-α,γ, TNF-α,β) from leukocytes

- Endogenous pyrogens (circulating cytokines), via blood → activation of the AA cascade in the preoptic area of the anterior hypothalamus and the third cerebral ventricle → release of PGE₂ from the hypothalamic endothelium (primary the capillary network of organum vasculosum of lamina terminalis) → stimulation of the 3rd receptor for PGE₂ (EP-3) on glial cells → release of cAMP → elevated set point → heat conservation and production → fever
Infectious agents
  Toxins
  Mediators of inflammations

Monocytes/Macrophages
  Endothelial cells
  Other cell types

Pyrogenic cytokines
  IL-1, TNF, IL-6, INF’s

Anterior hypothalamus

FEVER

↑ Heat conservation
↑ Heat production

Elevated thermoregulatory set points

PGE$_2$

Action of antipyretics
Other mechanisms of fever

- Vagal afferents transmit the pyrogenic signal to the hypothalamus, where they induce the release of norepinephrine and the activation of arachidonic acid cascade
- Direct activation of Toll–like receptors for microbial products (e.g. endotoxins), located on the hypothalamic endothelium → PGE₂ production and fever
- Local production by glial and neuronal cells of cytokines during a viral infection, CNS trauma or hemorrhage can also raise the hypothalamic set point and cause fever

Antipyretics

- Fever activates a negative feed back loop → release of endogenous antipyretics: vasopressin (V₁ receptor effect); CRH; α-MSH, IL-1 and TNF binding proteins, uromodulin
- Antipyretic drugs (NSAID e.g. acetylsalicylic acid, paracetamol, ibupofern) inhibit the enzymes COX1/ COX2 and PGE₂ formation
Stages of fever

1. *Stadium incrementi*
   ○ Core temperature rises to reach the new set point, heat production increased: cutaneous vasoconstriction, muscle activity increased, chills (goose bumps and shivering). The skin is pale, cold and dry. Shivering is an involuntary muscle activity when metabolic rate is increased 2-3 times the normal.

2. *Stadium acmes (fastigium)*, plateau phase
   ○ A balance between heat production and heat loss at a higher set-point. The skin is warm, flushed and dry

3. *Stadium decrementi*
   ○ The fever falls, the set level returns to normal, the body is too warm now → vasodilation and sweating
     ■ Fever subsides by lysis (progressively) or crisis (suddenly; often sudden increase before subsides: *perturbatio epicritica*)
1. Release of pyrogens in circulation

2. Reset hypothalamic control to high

3. Body responses that increase body temperature
   - Shiver (chills)
   - Vasconstriction in skin (pallor)
   - Increased BMR
   - Increased heart rate
   - Curl up body

4. Body reaches new high temperature
   - Feel warm

5. Treatment to remove pyrogens

6. Reset hypothalamus to normal

7. Body responses that increase heat loss
   - Vasodilation
   - Sweating
   - Lethargy
   - Extend body

8. Body returns to normal temperature
Types of fever

1. *Febris continua continens* (Continuous or sustained fever)
   ○ Sustained rise of the body temperature (in untreated typhus or typhoid) diurnal variation < 1 °C
2. *Febris continua remittens* (Remittent fever)
   ○ The temperature falls each day, but never to baseline, most fevers are remittent
3. *Febris continua intermittens* (Intermittent fever)
   ○ The temperature is normal in the morning, rising during the afternoon
     ■ Pyogenic infections (abscesses), lymphomas, miliary tuberculosis, bacterial endocarditis
     ■ Septic fever: a sharp rise and sharp fall in body temperature
**Febris continua continens**

**Febris continua remittens**

**Febris continua intermittens**
4. Periodic fever

○ Recurrences of fever that last from a few days to a few weeks and are separated by symptom-free intervals of varying duration

○ Can be caused by recurrent infection, malignancy or noninfectious inflammatory disorders (e.g. rheumatoid arthritis, Crohn’s disease)

○ Types of periodic fever
  ▪ Rat bite fever – *Streptobacillus, Spirillum minus*
  ▪ Fever every third day: malaria
    □ Fever related to cyclic development of parasites
    □ Alternate day fever: *plasmodium vivax*, or *ovale*
  ▪ Pel-Ebstein fever: in Hodgkin’s disease – bouts of fever and afebrile periods both lasting 3-10 days
  ▪ *Febris recurrens* (relapsing fever) is caused by various species of *Borrelia*
    □ Spirochetes are transmitted to humans by 2 vectors, ticks and lice w several episodes of high fever and afebrile periods, headaches, myalgia
Febris recurrens - Relapsing fever

Short febrile periods (3-6 days) occur between one or several days of normal temperature
- Undulant fever (Malta fever): Brucellosis
  - A worldwide zoonosis caused by the bacterial genus Brucella
  - Exposure to infected animals (cows, buffalo, camels, sheeps, pigs) and animal products (milk, meat) causes the disease in humans.
  - Fever – intermittent or undulant – is the most common symptom
  - Patients with acute brucellosis also have anorexia, insomnia, pain in the joints, bones and muscles, CNS symptoms
  - Symptoms may persist for months or years

- Familial Mediterranean fever (FMF)
  - An inherited disorder characterized by recurrent bouts of fever (38-40°C) and polyserositis (peritonitis, pleuritis, pericarditis), arthritis, and skin lesions
  - Nonsense or missense mutations in the MEFV (Mediterranean fever) gene in many cases, resulting in uninhibited activity of the neutrophil chemotactic factors (c5a, IL-8) and episodes of inflammation
  - Mutations are more common in particular ethnic groups, inhabitants of the Mediterranean basin
  - Renal amyloidosis may develop, which may lead to nephrotic syndrome and renal failure
    - Serum amyloid A, an acute phase protein is deposited in the kidneys
  - Treatment with prophylactic colchicine prevents acute attacks as well as renal amyloidosis in most patients.
Effects of fever

- Increase in heart rate (8-12 min/ °C)
  - Relative bradycardia: temperature-pulse dissociation, conditions where proportionate rise of pulse rate does not take place
    - Typhoid fever, brucellosis, leptospirosis, some drug-associated fevers, and many factitious fevers
    - Cardiac conduction abnormalities e.g. in acute rheumatic fever, viral myocarditis, bacterial endocarditis
  - Relative tachyarrhythmia: thyreotoxicosis, myocarditis
- Increase in respiration rate (2.5/min)
- Increase in metabolic rate (glucose, fat, protein catabolism),
- Acute phase response (due to the effect of cytokines)
  - Fever, hepatic synthesis of the acute phase proteins (e.g. CRP-C reactive protein, protease inhibitors, ceruloplasmin), leukocytosis, increase in slow wave sleep, anemia, muscle cell proteolysis
- Increased host immune defense
  - T and B lymphocyte proliferation, neutrophil granulocyte kemotaxis and killing
Detrimental aspects of fever

- Discomfort due to general malaise
- Muscle wasting and weight loss
- Febrile convulsions – in some children, especially those with a family history of epilepsy
- Delirium due to hyperpyrexia sweating: loss of salt and water → dehydration
- Heart failure in elderly patients with cardiac disease
- Respiratory failure in patients with abnormal lung function
Exogenous heat disorders – Hyperthermia

- Rise in core temperature **without elevation of the hypothalamic set point**
- Predisposing factors
  - Hot environment and/or severe physical effort (increase in heat production)
    - Hot waves leading to impaired heat dissipation
    - High ambient humidity / poorly ventilated places
  - Inappropriate clothing
  - Failure of the thermoregulatory control center:
    - infants, elderly, alcoholism, narcotics, neurologic-psychiatric diseases
  - Salt-water balance disorders
  - Disorders of sweating: lack of the glands or anticholinergic drugs
○ Increased heat production, altered metabolism: hyperthyroidism, pheochromocytoma, obesity
○ Congestive heart failure: e.g. elderly people
  ■ Heat loss impaired due to decreased CO, decreased internal heat flow (from the core to the skin) and incr. muscle activity and heat production caused by dyspnea
  ■ Treatment with diuretics leads to hypovolemia and impaired heat dissipation
○ Drug induced hyperthermia
  ■ Sympathomimetics, antihistamines, cocaine, amphetamine, ecstasy, lysergic acid diethylamide (LSD)
Types of hyperthermia (heat syndromes)

- Heat collapse (heat syncope)
- Heat exhaustion
- Heat stroke
- Malignant hyperthermia
- Neuroleptic malignant syndrome
- Serotonin syndrome
- Induced hyperthermia
Heat collapse (heat syncope)

- Hot environment and e.g. long-lasting standing: vasodilation (blood pooled to the legs), decreased venous return
- Sweating leads to volume depletion, decreased cardiac output, blood pressure, and brain perfusion leading to fainting
- Common in elderly patients receiving diuretics → salt and water depletion and impaired heat dissipation
- Symptoms and signs
  - Core temperature: normal, below normal or slightly elevated 37-39 °C
  - Skin: pale and cold due to increased sweating
Heat exhaustion

- Salt-water balance disorders due to heat exposure
  - Core temperature is normal or high, no tissue damage
- **Water-depletion heat exhaustion**: seen in acclimatized persons who have inadequate water intake during exposure to extreme heat and strenuous exercise
  - Excessive sweating, hypovolemia and hypernatremia might develop
- **Salt-depletion heat exhaustion**: Heat cramps (miner’s or stoker’s cramps)
  - If after intensive sweating only the loss of water, but not of the salt is replaced, hyponatremia might develop
  - Painful spasms of the voluntary muscles, after strenuous physical work in high ambient temperature caused by hyponatremia
    - Hyponatremia: fluid moves from EC to IC and brain; bradycardia, increased intracranial pressure, central vomiting, confusion, hypokalemia
Heat stroke

- Definition: a life-threatening illness with elevated core body temperature > 40°C
  - CNS dysfunction: delirium, convulsions, or coma
- Incidence: increases with global warming and with the frequency and intensity of heat waves
- Two distinct forms
  - Classic heat stroke
    - Common in children and elderly people: poor and socially isolated and/or with preexisting chronic disease e.g. congestive heart failure and treated with diuretics which causes volume depletion, impaired heat dissipation and sweating
  - Exertional heat injury
    - Strenuous exercise, high ambient temperature and humidity
    - Seen in runners with inadequate conditioning or improper hydration
Adaptation to heat stress
○ Activation of hypothalamic and peripheral heat receptors and hypothalamic thermoregulatory center
  ■ Increase in cardiac output (≈ 20 liters/min), tachycardia, vasodilation
    □ Heat loss due to incr. internal heat flow (shift of heated blood from the inner organs to the skin), and sweating

○ Acute-phase response to heat stress: inflammatory cells, mediators, cytokines are activated

○ Elevated levels of heat-shock proteins
  ■ Molecular chaperones – protect cells against heat injury by binding to proteins and preventing their irreversible denaturation
  ■ Central regulators of the baroreceptor-reflex response, abating hypotension and bradycardia → cardiovascular protection

○ Genetic factors → influence the adaptation to heat stress
  ■ Susceptibility to heat stroke: candidate susceptibility genes encode cytokines, coagulation proteins, heat-shock proteins
Pathogenesis of heat stroke: *heat stroke has many similarities with the sepsis syndrome*

- Heat has a direct cytotoxic effect
- Thermoregulatory failure coupled with an exaggerated inflammatory and coagulation response and the development of multiorgan dysfunction syndrome

1. Heat dissipation may be impaired due to the presence of predisposing factors e.g. heart failure, diuretics which decrease the cardiac output and impair the heat dissipation
2. Increased sweating during exposure to heat can lead to salt and water depletion, hypovolemia
3. Exaggeration of the acute-phase response due to bacterial translocation and endotoxemia
   - Strenuous exercise/ high ambient temperature
     - Blood shifts from the mesenteric circulation to the working muscles and the skin
     - Splanchnic hypoperfusion leads to altered barrier functions of the intestines and leakage of endotoxins which induce the production of inflammatory cytokines/ mediators, causing tissue hypoperfusion, hypotension, and decreased heat dissipation
4. Coagulation disorders and endothelial-cell injury in heat stroke
   ○ Physiological function of the endothelium
     ■ To regulate the vascular tone and permeability (NO/endothelin) and leukocyte migration
     ■ To keep the balance between procoagulant and anticoagulant substances
   ○ Hyperthermia: causes endothelial injury
     ■ Enhances vascular permeability and the leakage of fluid out of vessels
     ■ Increases the expression of adhesion molecules and the activation of leukocytes and platelets

5. Metabolic manifestations of heat stroke
   ○ Tissue damage results from uncoupling during oxidative phosphorylation and depletion of energy stores
     ■ Cell membranes become more permeable and sodium influx into cells is increased
       □ Accelerated sodium-potassium (ATPase) activity is required to pump sodium out of the cells resulting in more energy depletion
   ○ The declining energy reserves impair thermoregulatory mechanisms, and clinical signs of heat stroke appear
   ○ Proteins begin to denature at higher temperatures, with resultant widespread tissue necrosis, organ dysfunction, and organ failure
Clinical manifestations of heat stroke

○ Critical thermal maximum
  ■ A core temperature of 41.6 °C to 42 °C (for 45 minutes to 8 hours) causes cell death due to apoptosis – the induction of heat shock proteins is protective
  ■ 49 to 50 °C- cellular necrosis occurs

○ Failure of heat loss
  ■ Vasoconstriction, sweating ceases
  ■ Dry and hot skin

○ CNS dysfunction: confusion, disorientation, apathy, loss of consciousness, seizures, death

○ Cardiovascular system: tachycardia and hypotension

○ Respiratory system: tachypnea/hyperventillation

○ Acid-base and ion balance disorders: respiratory alkalosis and metabolic (lactic) acidosis
● Complications of heat stroke
  ○ Multiorgan-dysfunction syndrome
    ■ Encephalopathy, rhabdomyolysis, acute renal failure
    ■ Acute respiratory failure, ARDS
    ■ Myocardial depression, heart failure
    ■ Intestinal ischemia or infarction, hepatocellular and pancreatic injury
    ■ Hemorrhagic complications: DIC

● Sunstroke
  ○ Caused by direct sun radiation on head and neck
    ■ Nausea, headache, dizziness, cerebral hyperemia and serious meningitis – may be fatal
Malignant hyperthermia

- Genetic defects of sarcoplasmic Ca\(^{2+}\) transport and storage, in which the Ca\(^{2+}\) releasing channel (ryanodine receptor – Ryr1) is affected in 80 % of cases
- Incidence of the autosomal dominant form is 1:50 000 to 1:100 000, the individuals have no symptoms between the attacks; in the recessive form other congenital abnormalities (skeletal) are also present
- Pathogenesis
  - Inhalational anesthetics (halothane) or muscle relaxants (succinylcholine) cause sudden and excessive release of Ca\(^{2+}\) from sarcoplasmic reticulum
• Symptoms and signs
  ○ Generalized, uncoordinated muscle contractions, enormous heat production and rapidly rising hyperthermia (42 °C)
  ○ High oxygen consumption and anaerobic glycolysis
  ○ Metabolic acidosis, rhabdomyolysis, myoglobinuria
  ○ Hyperkalemia, tachycardia, arrhythmia, heart failure
  ○ Late complications: DIC, pulmonary edema, and acute renal failure

• Prevention and treatment of malignant hyperthermia
  ○ Thorough family history
  ○ Monitor the temperature of all patients under anesthesia
  ○ Spinal or epidural anesthesia by persons at risk
  ○ Discontinuation of the anesthetics and/or muscle relaxants
  ○ Cooling with ice
  ○ Dantrolene sodium → blocks Ca^{2+} release in skeletal muscles
Neuroleptic malignant syndrome

● Etiology: unknown, a variant of malignant hyperthermia (?)
  ○ Occurs after use of neuroleptics (e.g. haloperidol, phenothiazides) in therapeutic doses.

● Mechanism
  ○ Inhibition of central dopamine receptors in the thermoregulatory center

● Symptoms
  ○ Muscular rigidity
  ○ Hyperthermia: core temperature ~ 41.1 °C
  ○ Autonomic dysfunction: tachycardia, labile BP, profuse sweating, dyspnea, incontinence
  ○ Altered consciousness or coma
  ○ Mortality ~ 20% (due to renal failure and arrhythmias)
Serotonin syndrome, caused by
  ○ Serotonin reuptake inhibitors (SSRI)
  ○ Tricyclic antidepressants (TCA)
  ○ Amphetamine, cocaine, ecstasy
  ○ Symptoms: tremor, diarrhea, hyperthermia

Induced hyperthermia
  ○ Regional hyperthermia
    ■ A traditional, but unproved therapy for many musculoskeletal diseases and chronic respiratory infections
  ○ Whole-body hyperthermia
    ■ The adjunctive therapy of cancers - increase of BT to up to 42.4 °C
Disorders associated with low temperatures – hypothermia

- Pathomechanism
  - Mild to moderate cold exposure with thermoregulatory malfunction
  - Normal thermoregulation but extreme cold

- Predisposing factors
  - Prolonged exposure to extreme cold (especially if wet and windy)
  - Altered thermoregulation
    - Neurologic /psychiatric disorders
    - Alcohol or drug intoxication – barbiturates, benzodiazepines, opiates
    - Sepsis; uremia
    - Age: infants, elderly
    - Impaired peripheral thermal sensing (receptors, nerves)
    - Decreased metabolism and heat production: myxodema, malnutrition, pituitary insufficiency, Addison’s disease, hypoglycemia
Manifestations of hypothermia

- Accidental hypothermia
  - Local cold injuries
  - Generalized hypothermia
- Iatrogenic/ perioperative hypothermia
- Induced hypothermia
Local cold injuries

- Manifestations
  1. Frostnip: the mildest form
     ■ Earlobes, nose, cheeks, fingers, toes, hands, feet
  2. Immersion foot: trench foot – in shipwreck survivors or soldiers; wet, but not freezing cold
     ■ Stages: primary hypoxic trauma manifested as three distinct conditions
       □ 1. ischemia (pale, pulseless extremities) vasoconstriction, incr. blood viscosity
       □ 2. hyperemia: red, painful, swollen feet
       □ 3. posthyperemic period (recovery period)
3. Frostbite: freezing injuries

- When tissue freezes, ice crystals may form within or between the cells interfering with the sodium pump → rupture of the cell walls, RBCs clump, platelet aggregation, thrombosis

- Symptoms
  - Pallor, loss of sensation, blister formation (2nd degree); after days and weeks – extensive tissue necrosis and healing by scar (3rd degree)

- Complications
  - Muscular weakness, sensitivity to cold and pain, atrophy, ulceration, gangrene of superficial areas

- Therapy
  - Restoration of core temperature, gradual rewarming of the frostbitten limb by immersion in water
Generalized hypothermia

A core temperature below 35 °C

Stages of hypothermia

1. Stage of excitement (mild hypothermia 35-32 °C)
   ○ Maximal muscle tremor, metabolic rate increased, hyperglycemia
   ○ Incr. oxygen consumption; sympathetic activation → vasoconstriction
   ○ Cold, cyanotic extremities
   ○ Cardiac output, respiratory rate increased
   ○ Cold diuresis: due to peripheral vasoconstriction, the circulation is redistributed to central (vital organs), relative hypervolemia occurs, which in turn will activate the natriuretic hormones leading to hypovolemia
   ○ CNS symptoms: apathy, confusion, and disorientation
2. Stage of exhaustion (moderate hypothermia 32-28 °C)
   ○ Shivering ceases and the metabolic rate falls rapidly – hypoglycemia
   ○ Bradycardia, arrhythmia (atrial fibrillation, AV block)
   ○ Cardiac output and renal blood flow (RBF) decreased
   ○ Depressed breathing
   ○ CNS depression: confusion, disorientation, hyporeflexia

3. Stage of paralysis (severe hypothermia < 28 °C)
   ○ Coma, no pupillary reflexes
   ○ Circulatory arrest, asystole, ventricular fibrillation
   ○ Cold diuresis
   ○ Hypoxia of the peripheral tissues → lactic (metabolic) acidosis;
   ○ Hepatic and renal failure
   ○ Hematologic disorders: viscosity of blood increased, hemoconcentration, platelet dysfunction, DIC
Management of accidental hypothermia

- Gradual rewarming (a few °C per hour), if too rapid:
  - Rewarming shock
    - Peripheral vasodilation, fall in CO / BP, tissue hypoxia
  - After-drop phenomenon
    - Cold peripheral blood reaches rapidly the body core → hypothermia ↑

- Rewarming procedures: depend on the severity of hypothermia
  warm room, blankets, warm bath, electric blankets, warm infusion, hemodialysis, active warming by means of extracorporeal circulation

- Restoration of circulation:
  - anti-arrhythmic drugs and defibrillation
  - thrombolytic therapy, t-PA
Iatrogenic, peri/intra-operative hypothermia

- **Predisposing factors**
  - Immobilization, exposure to cold environment of the operating room
  - Low metabolic rate during surgery

- **Mechanisms**
  - **General anesthesia**
    - Anesthetics inhibit thermoregulation i.e. vasoconstriction and shivering
    - Anesthetized patients are poikilothermic (body temperature is determined by the environment)
    - Redistribution of body heat from the core to the skin surface
      - Heat loss by radiation and convection
  - **Regional anesthesia**
    - Nerve blocks impair the normal activation of regional thermoregulatory defenses (sweating, vasoconstriction, and shivering) and the central control of thermoregulation: lower core temperature are tolerated than normal
Induced hypothermia

- Local: cooling induces vasoconstriction, ameliorates the local signs of inflammation (redness, edema, pain)
- Generalized: cardiac/CNS surgery
  - Core temperature < 28 °C to protect the myocardium and CNS from hypoxia during circulatory arrest induced for the repair of different cardiac lesions or neurosurgery
  - Mechanism
    - Cooling/ and drugs administered peri-operatively (i.e. anesthetics, muscle relaxants) inhibit the thermoregulatory defense mechanisms of heat production (incr. metabolic rate, incr. muscle activity, sympathetic activation) → the stages of accidental hypothermia are bypassed, setting the core temperature below 28 °C
Induced hypothermia after cardiac arrest and ischemic stroke

- Can reduce the enzyme activity/cell metabolism and the extent of organ damage
- **Methods**
  - Surface cooling (e.g. cooling blankets)
  - Rapid induction of mild hypothermia: intravenous injection of large-volume ice-cold fluid
  - Intracarotid cold saline infusion: would allow the selective cooling of the brain
- **COOL-MI trial**: therapeutic cooling before angioplasty reduced the infarction size in patients with anterior-wall infarction
  - Further studies are needed for these methods to become a routine in clinical practice