MAYO CLINIC FLORIDA

TARGETED TEMPERATURE MANAGEMENT (TTM) GUIDELINES

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I. ELIGIBILITY/CONTRAINDICATIONS

Inclusion criteria:

- Successful post-cardiac arrest resuscitation, defined as a period of absent pulses requiring chest compressions, regardless of location or presenting rhythm followed by return of spontaneous circulation (ROSC) and a comatose state (i.e., not following commands) without other obvious reasons for coma (drug intoxication, pre-existing coma prior to arrest),[1-3] or
- Global cerebral edema refractory to osmotherapy and/or barbiturates (ICP>20mmHg or at the discretion of a neurointensivist),[4-6] or
- Refractory hepatic encephalopathy with global cerebral edema (ICP>20mmHg or at the discretion of a transplant critical care intensivists or via input with a neurointensivist) in liver failure patients undergoing liver transplant evaluation,[7] or
- Other cases of successful post-cardiac arrest resuscitation in which there is concomitant multi-organ dysfunction syndrome, severe sepsis, severe bleeding or vasopressor refractory shock, uncontrolled serious or life-threatening cardiac arrhythmias, recent major surgery within 14 days should be made on the individual basis based on the overall risk vs benefit of hypothermia. Cooling to 36˚C only may be advised in hemodynamically unstable post-cardiac arrest patients.[8]
- Code status discussion or clarification the time of hypothermia to be initiated or discussed with patient's proxy in case of a re-arrest.

Relative contraindications:

- Pregnancy (there are case reports with good outcomes);[9,10] consult Mayo OB on call.

Exclusion criteria:

- Brain death (caveat: atropine/epinephrine may cause falsely dilated, unreactive pupils). In cases of clinical uncertainty, continuance of hypothermia until resolution of drug effects

may be advised. Or serial neurological examinations over time may help determine which effects on pupils are transient vs underlying permanent brainstem injury.

- Active, unstable for hypothermia as judged by the attending physician (and documented).

II. PHYSIOLOGY

Acutely, ischemia is characterized by a deficiency in oxygen, ATP, and glucose.[11] Cerebral metabolic rate is a principal determinant of cerebral perfusion; it decreases by about 6-7% for every 1ºC drop in body temperature thereby reducing oxygen demand, preserving phosphate compounds and energy stores and preventing lactate production and development of acidosis.[11] Cerebral blood flow decreases in parallel with cerebral oxygen consumption during hypothermia suggesting the preservation of autoregulation.[12] Cerebral ischemia triggers a release in excitatory amino acids and glutamate, causing excitotoxicity.[13] ATP deficit results in the disruption of ion gradients with calcium influx leading to mitochondrial dysfunction and depolarization of neuronal cell membranes causing the release of glutamate into extracellular space, leading to neuronal hyperexcitability followed by neuronal injury and death.[13] Neuron exposure to excessive levels of excitatory amino acids leads to the stimulation of non-N-methyl-D-aspartic acid (NMDA) subtype glutamate receptors, resulting in a toxic level of extracellular acidosis. Excess glutamate also leads to acidosis in addition to increased intracellular calcium, potassium, protease activation, and the synthesis of nitric oxide (NO) and reactive oxygen species (ROS). Hypothermia is known to reduce the release of excitatory amino acids, prevent glutamate-induced increase in NO synthesis and suppresses NMDA receptor phosphorylation.[11, 13]

Subacutely, secondary injury mechanisms take place: reperfusion with ROS generation, inflammation, and cellular apoptosis leading to the disruption of the blood-brain barrier and edema formation.[13] Hypothermia blunts this response via attenuation of markers of oxidative and nitrosative stress; it also mitigates inflammatory reaction by reducing astrocyte and microglial activation and decreasing expression of inflammatory cytokines, endothelial molecules, and neutrophils.[11] Following ischemia-reperfusion injury and ensuing inflammation, cells may enter a pathway of programmed cell death or apoptosis.[14] Immediately following insult, neurons die by necrosis due to membrane disruption and excitotoxicity, whereas a subsequent wave of neuronal death occurs via an apoptotic pathway. Hypothermia attenuates the release of proapoptotic mediators and activates antiapoptotic pathways. One of the most important effects of hypothermia is the preservation of the blood-brain barrier following the disruptive effects of ischemia-reperfusion, traumatic injury, or even mannitol administration.[11] Hypothermia primarily prevents the activation of metalloproteinases that degrade the extracellular matrix and augments the expression of endogenous metalloproteinase inhibitors.

III. LOGISTICS

- For coma following cardiac arrest, the Mayo Hypothermia Service will be activated by either the ED physician or the Code Blue team; the Neurology resident and CCS resident on call should be consulted as soon as possible following the event.
- The role of the Neurology resident or team is to provide a coma evaluation to ensure the patient is truly comatose (ie., GCS 8 or less) and brainstem reflexes (FOUR score) exam before initiation of drugs that confound the neurological exam. The baseline examination is important for ultimate neurological prognostication. If the neurology resident is

unavailable due to other competing emergencies the ED or CCS team should document the neurological exam and coma present, document this exam and patient is eligible for hypothermia. The neurology CCS team will pick up the patient to follow for neurological prognostication.

- TTM should be initiated as soon as possible after cardiac arrest in comatose patients.
- If patient is in the ED, staff personnel should begin to implement TTM protocol until ICU bed is available.
- The device typically used for therapeutic temperature control available at Mayo Clinic Florida is the Arctic Sun (Bard Medical, Medivance Inc., Louisville, CO). The Artic sun SHOULD NOT BE USED AS A COOLING BLANKET. It is indicated only for induction of hypothermia or maintenance of hypothermia. The cost is ~$900 per pad set.

IV. TTM STEPS/PROTOCOL

Preparation

- Arterial line should be placed while initiating cooling as may it be more difficult to place once the patient reaches target temperature
- Urgent Cardiology consultation for PCI if indicated
- Evaluation for alternative causes of arrest
- Baseline Neurological Evaluation
    a. Exclude other causes of coma (mass lesions, metabolic coma, seizures etc.)
    b. Document Glasgow Coma Score
    c. Examination by neurology team prior to induction of hypothermia, sedation and paralysis; re-examination by neuroCCS team following return to normothermia and cessation of sedation and paralysis
- Obtain initial labwork (see CCS Hypothermia Order set, ordered by CCS team):
    a. ABG, CBC / PT / PTT/INR, Fibrinogen
    b. Renal panel, iCa / Mg / Phos
    c. Lactate/CPK-MB/CK/Troponin
    d. Cortisol level (as indicated)
    e. Urinalysis
    f. Blood Cultures, Urine Culture, and Sputum Culture (if appropriate)
    g. Toxicology screen if appropriate
    h. Amylase, Lipase, LFTs
    i. Beta HCG on all women of child-bearing age
    j. Neuron-specific enolase (NSE) +24 hrs offset for neurological prognostication
- Sedation
    a. Sedation will be initiated PRIOR to induction of paralysis
    b. Midazolam 0.01-0.03 mg/kg IV bolus, then titrate infusion to 0.02-0.1 mg/kg/hr
    c. Propofol 20 mcg/kg/min IV, then titrate to 30-50 mcg/kg/min IV
    d. Goal Ramsay score 4
    e. Sedation will continue uninterrupted while patient is paralyzed

- Paralysis if cooling below 36°C induces shivering. If shivering does not occur, do not use neuromuscular blockade
    a. Cisatracurium 0.2 mg/kg bolus followed by an infusion up to 0.3 mg/kg-hr
    b. Titrate paralysis to shiver suppression or a 2/4 TOF every 1 hour
    c. Lubricate eyes; ensure eyes are not spontaneously open to prevent corneal injury
    d. Paralysis to be maintained until patient rewarmed to core temperature >35°C

Monitoring

- Continuous core temperature by bladder thermistor (Bard Criticore catheter)
- Blood pressure by arterial line and cuff
- Telemetry
- Pulse oximetry
- CVP measurement at the discretion of CCS
- ICP monitor at the discretion of the neurologist/neurosurgeon, place PRIOR to induction of hypothermia for refractory intracranial hypertension
- EEG monitoring at the discretion of neurology team or neurointensivist, especially if myoclonic jerks or activity suspicious for seizure is present prior to neuromuscular blockade, or for prognostication.

Nursing care

- Monitor temperature every 15 minutes during induction of hypothermia, then every hour during maintenance
- Document RASS every 30 minutes during induction and then every hour during maintenance
- Measure and document Bedside Shiver Scale (under Complex Assessment, iView, Hypothermia) Notify MD of any shiver requiring additional medication orders.
- Monitor and document the degree of shivering using the Bedside Shiver Scale (Under Complex Assessment, Hypothermia)
- Train of four (TOF) every hour while paralyzed at wrist (median or ulnar) with ECG sensors and cables. Do not use orbicularis oculi (around eye) as this is potentially direct muscle stimulation. Goal TOF is 2/4 twitches.
- Vital signs and device temperature every hour
- Daily GCS and FOUR score
- Check skin for burns every two hours when using cooling blankets and ice packs; every six hours when using Arctic Sun

Orders

- Ventilator bundle – HOB>30°, mouth care with antibiotic brushes Q1hr, etc.
- Sedation and paralysis remain until rewarmed >36 °C
- Stress Ulcer prophylaxis with either proton pump inhibitor (unless cardiac stent placed in which case H2 blocker like ranitidine 150mg NGT BID may be used)
- DVT prophylaxis with heparin SQ or equivalent
- Control hyperglycemia, goal serum blood glucose < 150. Insulin use may exacerbate hypokalemia.

- 12 lead EKG every eight hours during cooling for at least the first 24hrs, then per discretion of Cardiology or Critical care Services
- Serum electrolytes, magnesium, ionized calcium, ABG, phosphorous, lactate every 8 hours during cooling. Beware of hypokalemia during cooling and hyperkalemia during rewarming; treat to maintain normal potassium, monitoring more often if needed.
- CBC with differential and PT/PTT every 12 hours during cooling
- Blood culture, one central and one peripheral, and urine culture every 12 hours during cooling. High volume blood cultures only if antibiotics are concomitantly administered.
- Daily ABG, CXR, CHEM7, CBC, PT/PTT, I/O, weight

Ventilation

- Oxygenation: maintain SpO_2>92%, PaO_2>65. Adjust FiO2 and PEEP to avoid excessive oxygenation as O2 consumption decreases with cooling; hyperoxia in cardiac arrest patients has been linked with worse outcomes.[15]
- Ventilation: maintain normal pH
- Avoid PEEP > 5 cmH_2O in those patients with known or suspected elevated intracranial pressure (ICP). In those with ICP monitors, PEEP can be titrated as needed for the lungs and PaO2 while monitoring ICP.

Cooling

- Arctic Sun instructions: the Arctic Sun Temperature Management System is a water-based, non-invasive thermoregulatory device that monitors and automatically controls patient temperature within a range of 33°C to 37°C (91.4°F to 98.6°F). The Arctic Sun System consists of the Control Module and single-use Energy Transfer Pads.
- Application of pads: Control module:





The temperature feedback from the patient is supplied to the control module using a bladder thermistor (Bard Criticore catheter)

- Alternatives if Artic Sun device not available:

a. Obtain two cooling blankets with the Cincinnati SubZero Blanketrol II and "sandwich" the patient. Place sheets between the patient's skin and the blankets
b. Use ice packs in the patients groin chest, axilla, and side of neck; avoid packing ice on top of chest; that may impair chest wall motion. Check skin integrity continuously and constantly rotate ice packs to prevent cold thermal injury.
c. Cold saline infusion, 30 cc/kg of 4º C normal saline over 30 minutes, can be performed via a peripheral line or central venous catheter (order available in Powerchart)
d. Once goal temperature is reached, ice bags may be removed and the cooling blankets or Artic Sun used to maintain temperature

- Temperature goals
    e. Cool to a goal of 33°C for hypothermia for 12 to 24 hours; in unstable patients goal of 36°C is acceptable, then slow rewarming can commence (0.5°C every two hours).
    f. If patient is truly hemodynamically unstable at 33C (Torsades, or 2-3 vasopressor refractory shock), set a target temp of 34. If the same results are at 34C, then consider 36C based on the recent study.[8]
- Shiver control
    g. Goal is complete shiver suppression (Bedside Shiver Scale = 0). If shivering not controlled within one hour, initiate paralysis
    h. Meperidine IV 12.5 to 25 mg loading dose followed by an infusion of 12.5-25 mg/h. Meperidine can be combined with dexmedetomidine or buspirone for additive or synergistic effects, respectively, in lowering the shivering threshold. Meperidine can cause sedation, seizures, and central nervous system toxicity. Do not use if renal failure/oliguria present or patient taking SSRI or MAO inhibitor.
    i. Apply heated polyvinyl chloride (PVC)-lined boots and mittens to hands and feet which are sensory 'tricks' that help reduce CNS perception of cold
    j. Apply a warming blanket (e.g., Bear Hugger) that circulates warm air inside the blanket OVER the patient's body (can be over the Artic sun). This simply reduces shiver by altering sensory perception of cold and should not alter core temperature on the cooling device
    k. Oral buspirone 30 mg every 8 hours orally or by nasogastric tube if shivering or hypothermia is prolonged more than 24hrs
    l. In mechanically ventilated patients, sedative infusion rate (propofol, fentanyl, dexmedetomidine) can be increased, and if refractory, competitive neuromuscular blocking agents can be administered with sufficient sedation.
- Blood pressure management
    m. Target SBP > 90, MAP > 80 mmHg. Target CVP > 4-6 mmHg. These should be individualized based on various specialist input and underlying comorbidities of the patient
    n. All patients will be volume resuscitated as determined by usual assessment of cardiac performance. Induced diuresis will not be performed when cerebral edema is suspected

o. Vasopressors if unresponsive to volume resuscitation. Choice of pressors dependent upon etiology of shock, consider vasodilatory and cardiogenic shock. Consider IABP for refractory cardiogenic shock
p. In all patients, mannitol or other hyperosmolar drug therapies will not be administered unless there is evidence of deterioration by neurological examination or by CT scan of the head

- Rewarming
  b. Passive – remove device and/or cooling blankets (may take 8 hours).
  c. Active – set device to rewarm by 0.5°C every 2 hours.
  d. Maintain paralytic and sedation until temperature of 36°C is reached: first discontinue the paralysis; sedation may be discontinued once a train of 4 is achieved.

V. EFFECTS BY ORGAN SYSTEM

- ***Cardiac:***
  - A decrease in heart rate parallels that in temperature with an average heart rate of about 40-45 beats per minute at 32ºC (this is a normal response).[11]
  - Positive inotropic effect: ↓HR= better LV filling; therefore, augmentation of HR is not recommended in stable patients; rewarm to a higher temperature if unstable.
  - Risk of arrhythmias generally does not increase at temperatures above 30ºC.[11]
  - ↑ Systemic vascular resistance from hypothermia-induced peripheral vasoconstriction ➔ ↑ venous return ➔ANP activation ➔ ↓ADH ➔ "cold diuresis" (especially if getting mannitol); it should be treated aggressively with fluid and electrolyte repletion. Magnesium, phosphorus and potassium should be monitored closely and maintained in the normal range (because it will rebound to a higher value during rewarming).
  - Re-warming too rapidly can cause vasodilation, hypotension, and rapid electrolyte shifts (beware of hyperkalemia)
- ***Pulmonary:***
  - Hypothermia shifts the oxyhemoglobin curve to the left, which may result in decreased O_2 delivery. This is offset by a concomitant increase in solubility of oxygen at decreased temperatures.[16]
  - With decreased metabolism, O_2 consumption/CO_2 production is decreased. Ventilator settings will need to be adjusted accordingly.
  - Shivering increases O_2 consumption and may negate the benefits of induced hypothermia. Thus, shivering must be prevented during hypothermia and is best accomplished by initiating neuromuscular paralysis prior to induction of hypothermia. If paralysis is begun well after hypothermia has been initiated it can result in a precipitous drop in core body temperature. Elderly patients will cool more quickly than younger or obese patients.
- ***Hematologic:***
  - Hypothermia can induce an in vivo coagulopathy which is not detectable by laboratory testing (as blood is warmed during testing).
  - Coagulation cascade is affected at temperatures below 33ºC, whereas platelet function may be decreased below 35ºC.[11]
- ***Renal, endocrine and gastrointestinal effects:***

- Hypothermia can decrease insulin sensitivity and lead to a reduction in insulin secretion, resulting in hyperglycemia, particularly during the induction stage. Hypoglycemia may occur if rewarming is too rapid.
- Potassium levels decline with hypothermia and are one of the reasons why slow rewarming is advised. Myocardium sensitivity to potassium is increased in hypothermia; therefore, hypokalemia may have a protective effect.
- Hypothermia may promote ileus and delayed gastric emptying.

- ***Infection risks:***
  - Hypothermia inhibits leukocyte migration/phagocytosis; no correlation has been found between increased infections and worse outcomes.[17]
  - May increase the risk of wound infections; therefore, need extra care to prevent bedsores and close monitoring of any catheter insertion sites is paramount.[11]
- ***Drug metabolism:***
  - Hypothermia-induced reductions in clearance have been shown for a number of commonly used ICU sedatives such as propofol; opiates such as fentanyl and morphine; midazolam; neuromuscular blocking agents such as vecuronium and rocuronium; and other drugs such as phenytoin. There is a decreased receptor response to morphine during hypothermia. During the cooling phase, the morphine dosage may need to be escalated to achieve adequate effect. However, during the rewarming phase, if the morphine dosage is not titrated downward, toxicity may occur.

Rebound hyperthermia may occur following rewarming; close temperature monitoring and maintenance of normothermia with cooling blankets as needed is paramount to continue neuroprotection.

POTENTIAL LABORATORY ABNORMALITIES ASSOCIATED WITH HYPOTHERMIA:

Potential Lab Abnormality	**Treatment**
Increased amylase	No intervention unless persistent after rewarming
Increased LFTs	No intervention unless persistent after rewarming
Increased serum glucose	Follow insulin protocol
Decreased K+, Mg, Phos, Ca	Correct as needed
Increased lactate	Optimize oxygen delivery
Metabolic acidosis	Optimize oxygen delivery
Thrombocytopenia	Correct if active bleeding
Leukopenia	No intervention unless persistent after rewarming

Increased PT/PTT	Correct if active bleeding

Temperature Conversion Table

Celsius	Fahrenheit
38.9	102
38.3	101
38.0	100.4
37.0	98.6
36.0	96.8
35.0	95.0
34.0	93.2
33.0	91.4
32.0	89.6
31.0	87.8
30.0	86.0

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