Targeted Temperature Management: Normothermia for Neuroprotection

I. Rationale

Elevated body temperature is associated with increased cerebral metabolic rate and associated metabolic demand, which can be deleterious to the brain and other organs in certain circumstances. The Targeted Temperature Management (TTM): Normothermia for Neuroprotection guideline can be used to induce and/or maintain normothermia in patients who are refractory to conventional fever treatment. The TTM: Hypothermia after cardiac arrest (HACA) and the TTM: Normothermia after cardiac arrest (NACA) guidelines should be used for patients who suffer cardiac arrest with return of spontaneous circulation.

**TTM: Normothermia for Neuroprotection**

This guideline section provides alternatives on management of fever refractory to standard initial interventions. Current literature supports that hyperthermia can exacerbate neural injury in brain ischemia and trauma. Aggressive fever control has been proved feasible, however its impact on long-term neurological outcomes remains undetermined. This guideline also specifically focuses on the management of shivering. Shivering is the most common side effect of TTM, and it is associated with increased brain metabolism and potentially eliminates benefits achieved with hypothermia.

Normothermia typically avoids the use of paralytics, although some patients may require medications for shivering suppression. Sedation requirements are usually low for normothermia. However, normothermia also requires experience and knowledge in the identification and pharmacologic management of shivering, including micro-shivering.

**General approach and intensity of therapy**

Once a goal temperature is determined by the clinical team, a graded intensity of therapy should be determined. Initial interventions to achieve normothermia in cases of fever include standing acetaminophen 650mg every 4 hours and cooling blankets. An intravenous cold saline bolus administered through a peripheral IV catheter can be considered as a following step, and a bladder temperature catheter should be used for continuous temperature measurement. If these measures are ineffective, an external cooling device is indicated.

II. Patient eligibility

1. Presence of refractory fever (T >= 38°C or 101°F) by reliable and reproducible means, including superficial artery temporal artery probe, continuously bladder temperature measurement or esophageal temperature measurement. A refractory fever is defined as not responding within a few hours to initial therapy with acetaminophen 650 mg every 4 hours, cooling blankets and ice packs.
2. The patient must undergo an appropriate infectious disease work-up and anti-microbial therapy initiated if indicated.
3. Alternative sources of fever should be investigated as appropriate, including lines/catheters, medications, deep venous thrombosis, cholecystitis, pancreatitis, sinusitis, etc.

III. Relative Exclusion Criteria

1. Contraindications to induced temperature reduction are patients with known hematological dyscrasias which affect thrombosis, (cryoglobulinemia, sickle cell disease, serum cold agglutinins), or known deep venous thrombosis (for femoral catheter approach only)
2. Peripheral vasospastic disorders
3. Contraindication for central venous catheter placement (for catheter-based approach only)
4. Known or suspected diagnosis of heparin induced thrombocytopenia (for catheter-based approach only).
5. Extensive skin defects (for cooling vest approach only)
6. Diagnosis of sepsis syndrome

IV. Procedure for normothermia for neuroprotection

1. All patients with refractory fever will be identified and a bladder or esophageal temperature probe will be placed.
2. Normothermia for neuroprotection target is 37.0 ± 0.5°C (97.5-99.5°F).
3. Ventilator warming device temperatures will be maintained at ≤ 37°C.
4. Tylenol 650mg q6 hours around the clock is given (if no patient contraindication).
5. Surveillance cultures from blood, urine, sputum, stool, and CSF (if applicable) will be sent if clinical suspicion for infectious etiology as source of fever.
6. Normothermia will be maintained continuously and assessment of fever burden reviewed each 24 hours period. Fever burden is considered to be the number of times the device intervened to manage a temperature elevation. The need for ongoing temperature control will be reassessed based on fever burden and patient need.

V. Methods

A. Cold Saline (optional)

Cold saline chilled to 4°C has been used to lower temperature during TTM therapy. At the discretion of the treating team, it may also be useful in “breaking” high fever in neurologically impaired patients. However, the administration via an internal jugular or subclavian venous catheter is unsafe due to the risk of dysrhythmia and contraindicated if a TTM device is in use.

Materials needed:
1. Foley catheter temperature device or esophageal temperature device and temporal artery thermometer
2. Chilled 0.9% Normal Saline at 4°C from medication refrigerator.
3. Patient weight determines the amount of saline delivered:
   a. Calculation is 30cc/kg infused intravenously over 30-45 minutes up to a maximum of volume of 1-2L.
b. Careful clinical consideration is advised in cases of cardiogenic shock or left ventricle failure.

4. **Peripheral IV access recommended.** Cold Saline should be delivered through a peripheral line. There are case reports of chilled saline through a subclavian and internal jugular central venous catheter causing life-threatening arrhythmia. Delivery by a femoral venous line may be acceptable if no peripheral access is available.

**Procedure:**
1. Place catheter and record the temporal artery thermometer and/or bladder/esophageal temperature on the flow sheet.
2. Set up first liter of Normal Saline on large bore tubing and into a pressure bag for delivery into a peripheral I.V. Total cold normal saline fluid volume is calculated as 30cc/kg, run over 30-45 minutes.
3. Cold Saline should be given via a peripheral line.
4. Record temperature every 10 minutes during infusion and up to 30 minutes after.

**B. Maintenance Cooling with an external cooling pad device:**
1. Eligibility confirmed and materials gathered.
2. Place continuous temperature device and place cooling pads on patient. Pad size is determined by weight and height.
3. After applying pads, set target goal ordered for specific normothermia guideline
   a. These pads may be used with external pacing pads. Place the external pacing pads on the chest and cover with Arctic sun pads.
4. Place Bair Hugger over patient and set on low.
5. Start magnesium sulfate IV bolus (2g over 30 minutes) for a goal level of 3.0 - 4.5 mEq/dL, followed by a Magnesium sulfate infusion (initial maintenance rate: 1g/hr which is equivalent to 25mL/hr).
6. Record temporal artery temperature, patient temperature from continuous device and water temperature of the device q1-2hrs.
7. Assess for shivering and treat aggressively with counter measures and/or medication.
9. Follow and document fever burden (how many times patient had fever for 24 hour period)
10. Determine discontinuation based on fever burden.

**C. Shivering management:**
Shivering may be encountered while maintaining normothermia, increasing metabolism and counteracting the benefit of targeted temperature management significantly. Shivering is evident on exam or should be suspected when water temperature of the device drops and remains low for a period over two hours. The shivering scale is a 5-step score ranging from no shivering to refractory shivering (see below).

**Shivering scale and recommended interventions:**
0. No shivering:
- Begin standing acetaminophen
- Forced air convection warmer (Bair Hugger) on low setting
- Begin magnesium sulfate IV bolus (2g) over 30 minutes for a goal level of 3-4.5 mEq/dL followed by a Magnesium sulfate infusion (Initial Maintenance Rate: 1g/hr which is equivalent to 25mL/hr).
- Magnesium sulfate is contraindicated in cases of renal insufficiency (calculated creatinine clearance rate < 30ml/min), neuromuscular junction disorders, second or third degree heart block, hyperkalemia (K >6mmol/L) or hypocalcemia (Ca <1.1 mmol/L).

1. Shivering <5 min:
- Forced air convection warmer (Bair Hugger) on high setting
- Meperidine intermittent IV push 12.5-50 mg as needed not to exceed 100mg every 6 hours. Contraindicated in the setting of renal insufficiency (serum creatinine ≥ 1.5) or with the concomitant use of monoamine oxidase inhibitors MAOI within the past 2 weeks.
- Buspirone 5 mg PO 2-3 times a day OR 7.5 mg PO twice a day; may increase the dosage by 5 mg/day every 2-3 days as needed (usual dose 20-30 mg/day 2-3 divided doses, MAX dose 60 mg/day)

2. Shivering sustained for >5 min after above interventions attempted:
- Meperidine infusion 12.5-50 mg/hr
- Propofol infusion at 10-300 mg/hr

3. Breakthrough shivering:
- Consider infusion of dexmedetomidine 1 mcg/kg over 10 min. Maintenance infusion dose range is 0.2-0.7 mcg/kg/hr
- Dantrolene. 50mg PO 2-3 times a day; may increase the dosage by 25-75 mg/day every 2-3 days as needed; maximum dose 400mg a day.

4. Refractory shivering:
- Neuromuscular paralysis with cisatricurium, vecuronium or discontinue TTM.

D. Discontinuation of normothermia:
Fever burden may be used to evaluate the continued need for targeted temperature management. There is no specific data to guide discontinuation of therapy, but consideration should be given to the risk-benefit ratio of the intervention for the patient.

VI. References

VII. Authoring Information

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Management Steps for Shivering

0: No shivering
- Tylenol - lowers hypothalamic set point
- Magnesium - promotes vasodilatation/causes hypotension
- Bair hugger - forced air-warming increases surface temperature without significant changes in core temperature

1: <5 min shivering
- Demerol - lowers shivering threshold/ decreases seizure threshold
- Buspirone - lowers shivering threshold/ works more effectively in conjunction with other meds.

2: >5min shivering
- Demerol infusion
- Propofol - promotes mild vasoconstriction/ causes hypotension

3: Breakthrough shivering
- Dexmedetomidine - manages vasoconstriction and shivering/ causes bradycardia
- Dantrolene - decreases muscle catabolism /flushing, AV block, drowsiness

4: Refractory shivering
- Paralytics - muscle relaxant, loss of exam, increased pneumonia rates
Shivering Scale and Management

No Shivering
(0)
Tylenol ATC
Bair Hugger on low Magnesium infusion

< 5 minutes
(1)
Bair Hugger on high Meperidine bolus Buspirone

> 5 minutes
(2)
Meperidine or Propofol infusion

Breakthrough Shiver> 5 minutes
(3)
Dexmedetomidine Dantrolene

Refractory shivering
(4)
Cisatracurium or Vecuronium