P-ICECAP: Cooling Basics, Clinical Issues and Cooling Protocol

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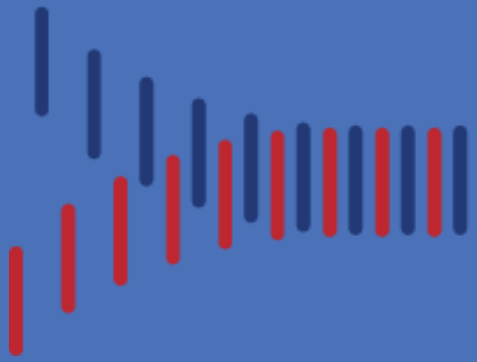
P-ICECAP



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Supported by UH3 HL159134, U24 HL159132

Overview

- This talk reviews basic temperature (temp) related information needed for RCs and site PIs.
- This will assist research teams in optimal temp control in our P-ICECAP patients. Periodic review should be done during the trial.
- ‘Just in time’ reviews with your clinical teams will be optimal, especially for the Induction and the Rewarming phases in P-ICECAP.
- You need to be your site’s TTM experts!
- Multiple Kahoot Questions

Outline

- Definitions
- Thermoregulation - basics
- Physiologic and other clinical effects of hypothermia/cooling
- Central temperature measurement
- Factors impacting target temperature
- Cooling protocol through 120 hours
- Case Examples (Temperature Curves)

Definitions

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Table 1. Proposed terms and definitions surrounding therapeutic hypothermia

Therapeutic temperature management definitions	
Hypothermia	Core temperature <36.0°C regardless of the cause
Induced hypothermia	An intentional reduction of a patients' core temperature below 36.0°C
Therapeutic hypothermia	Controlled induced hypothermia: i.e., induced hypothermia with the potentially deleterious effects, such as shivering, being controlled or suppressed
Controlled normothermia/therapeutic normothermia	Bringing down core temperature in a patient with fever, and maintaining temperature within a range of 36.0°C–37.5°C, with the potentially deleterious effects, such as shivering, being controlled or suppressed
Temperature range definitions	
Mild therapeutic hypothermia	An intentional and controlled reduction of a patients' core temperature to 34.0°C–35.9°C
Moderate therapeutic hypothermia	An intentional and controlled reduction of a patients' core temperature to 32.0°C–33.9°C
Moderate/deep therapeutic hypothermia	An intentional and controlled reduction of a patients' core temperature to 30.0°C–31.9°C
Deep therapeutic hypothermia	An intentional and controlled reduction of a patients' core temperature to <30.0°C
Mild hyperthermia	Core temperature 37.5°C–38.0°C
Moderate hyperthermia	Core temperature 38.1°C–38.5°C
Moderate/severe hyperthermia	Core temperature 38.6°C–38.9°C
Severe hyperthermia	Core temperature ≥39.0°C

TEMPERATURE CONTROL SYSTEMS. A complex system is needed to monitor and regulate the heat exchanges that occur

Table 71-1. Fahrenheit to Celsius Temperature Conversions

°C	°F
45	113.0
44	111.2
43	109.4
42	107.6
41	105.8
40	104.0
39	102.2
38	100.4
37	98.6
36	96.8
35	95.0
34	93.2
33	91.4
32	89.6
31	87.8
30	86.0
28	82.4
26	78.8
25	77.0
24	75.2
23	73.4
22	71.6
21	69.8
20	68.0

Therapeutic Normothermia
= Normothermia
TTM 36.0-37.5°C (36.8)

Therapeutic Hypothermia
= Cooling
TTM 32.0-34.0°C (33.0)

***Concern for arrhythmias at temp < 30°C. Rewarm STAT to goal**

****Greatly** increased risk of VF and other arrhythmias < 28°C. STAT rewarming required.**

Irwin and Rippe. Intensive Care Medicine, 4th ed, 1999

Thermoregulation Basics 101

Normal thermoregulation

- Heat production
  - Normal heat production from metabolic processes in liver, viscera, and muscle
  - During exercise or shivering, muscle primary source of heat generation, may be very large
- Heat elimination
  - Radiation = heat from skin to object without contact (NA)
  - Convection = airflow across skin (minor P-ICECAP)
  - Conduction = skin to object in contact (#1 in P-ICECAP)
  - Evaporation = sweating (NA in P-ICECAP)

Normal thermoregulation

- Hypothalamus regulates body Tº
  - Afferent inputs to hypothalamus
    - Skin*, abdomen, thorax, spinal cord, brain
  - Hypothalamus processes based on its temp setpoint
  - Central temp below hypothalamic setpoint results in efferent responses
    - Cutaneous vasoconstriction
      - impedes heat transfer through skin
    - Shivering
      - generates heat (muscles)

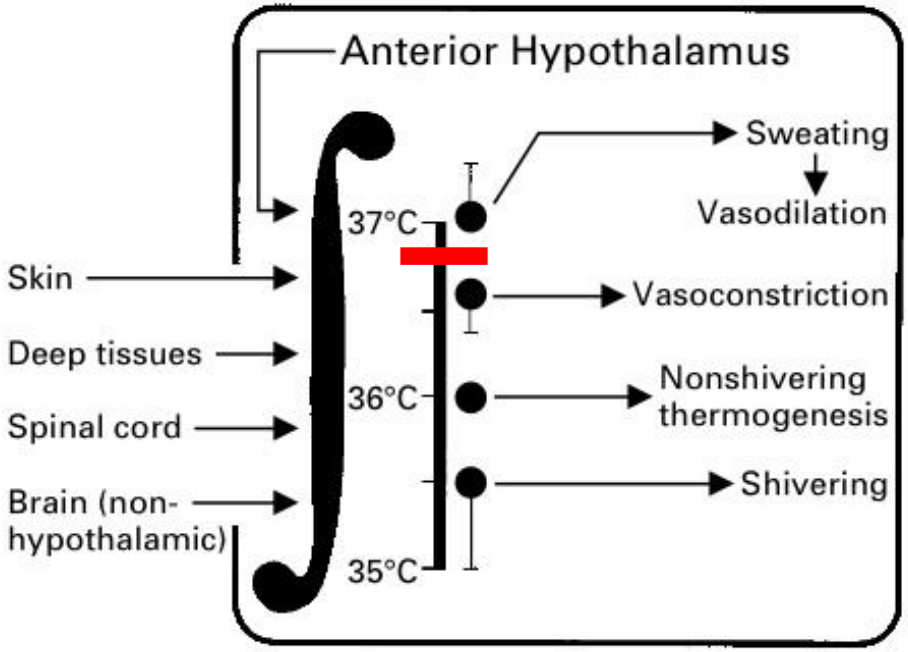

Figure 1. Thermoregulatory Control by the Hypothalamus.

The hypothalamus, the primary thermoregulatory control center in mammals, is shown as a large square. The skin surface, deep abdominal and thoracic tissue, spinal cord, and nonhypothalamic portions of the brain each contribute very roughly 20 percent of the input that is integrated by the hypothalamus in the control of autonomic thermoregulatory defenses (this input is shown entering the hypothalamus from the left of the figure). The temperature of the hypothalamus itself also contributes roughly 20 percent of the information used in thermoregulatory control. In the hypothalamus, the integrated body temperature is compared with threshold temperatures that trigger specific thermoregulatory responses. Values higher than the threshold for responses to warmth (i.e., sweating) or lower than the threshold for responses to cold (i.e., vasoconstriction and shivering) initiate the appropriate defense. Values between the thresholds for sweating and vasoconstriction lie in the interthreshold range — the range of temperatures that do not trigger any thermoregulatory defenses. The interthreshold range is normally only 0.2°C. Because thermoregulatory defenses are generally effective, human body temperature rarely deviates more than a few 10ths of a degree from the target value set by the hypothalamus. The thresholds for sweating, vasoconstriction, and shivering are from Lopez et al.[6] and are shown as means ±SD. The threshold for nonshivering thermogenesis is an estimated value.

Red bar = hypothalamic set point

Sessler DI. NEJM 1997:336;1730-7

Thermoregulation

- Pediatrics
  - Smaller infants / children
    - Larger SA/volume compared to adults
    - Reduced shivering response < 1 yr
    - Easier/shorter time to induce hypothermia (cooling) and temp control in very young
- Shivering decreases at approximately 33.5ºC
  - P-ICECAP goal 33.0ºC in hypothermia (cooled) groups

Normal thermoregulation

- Normothermia Phase
  - If hypothalamic set point is elevated (e.g., fever at 39ºC) relative to a goal temp 36.8ºC, one will see similar physiologic responses as Therapeutic Hypothermia (cooling) induction phase
    - Vasoconstriction
    - Shivering
  - Common etiologies of increased set point (fever)
    - Post-cardiac arrest syndrome
    - Infection
- Normal temp range is ~36.5-37.5ºC during a day.
  - Cooling devices sensitive to approx. $\pm$ 0.2ºC from their set point.
  - They will attempt to warm and cool normal subjects!

Physiologic and other effects of cooling in P-ICECAP

List of Physiologic Effects

1. Shivering
2. Hypovolemia (during cooling and rewarming)
3. CV including bradycardia
4. Potassium
5. Glucose
6. Other chemistries (Mg, PO4, etc.)
7. LFTs, amylase/lipase, lactate
8. Plts/Coags
9. WBC/Inflammation/Infection
10. Drug metabolism
11. Metabolic rate
12. Blood gases
13. Skin

Modified from:
- Polderman, CCM 2009
- ILCOR, Circulation, 2008

1. Shivering

- Causes large amount of heat generation/rewarming
- May or may not be visible
- #1 cause of poor TTM control in P-ICECAP
- Cooling devices may not overcome shivering (examples)
- Tx is REQUIRED. Not optional.
- Suggested agents
  - Opioids (e.g., fentanyl)
  - Benzodiazepines (e.g., midazolam), dexmedetomidine and others
  - NMB (e.g., vecuronium)
- Shivering response decreases at ~ 33.5ºC
- Shivering response less in young (< 1 yr)
- Will see shivering in <u>both</u> hypothermia (cooled) and normothermia phases, if hypothalamic set point is greater than goal temperature

1. Shivering – drugs to inhibit

- Benzodiazepines* (midazolam - example)
  - Sedative
  - Vasodilation (+/-)
  - Antiepileptic effects
  - Decrease shivering
- Opiods* (fentanyl - example)
  - Analgesia, sedation
  - Vasodilation (+/-)
  - Decrease shivering
- NMB* (vecuronium, rocuronium and others). Recall Cis-Atracurium has temperature dependent metabolism, prolonged with cooling (Hofmann Reaction). Twitch monitoring with NMB infusions recommended.
  - Inhibits shivering, greatly facilitates cooling and temp control
  - Masks sedation level and seizures

*ILCOR, Circulation 2008 – drug classes recommended

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Induction of Hypothermia without sedation

- If hypothalamic set point normal at 37.0ºC
  - Vasoconstriction - 36.5ºC
  - Shivering - 35.5ºC
  - ↑HR
  - ↑Metabolic rate (40-100%)
  - ↑Stress response
- Undesirable in patients with neurologic and/or CV injury post arrest

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Induction of Hypothermia with sedation/analgesia

- ↓Shivering
- ↓HR
- ↓ Metabolic rate
- ↓ Stress response
- Improved neurologic outcome compared to no sedation/analgesia.
- Less CV stress in post arrest patient

2. CV: Hypovolemia

- Hypovolemia – common during the cooling Induction Phase
  - Often due to cold diuresis (renal);
  - Results in tachycardia and hypotension;
  - Requires tx
  - Note: if patient cooled and HR not reduced, may be sign of hypovolemia
- Hypovolemia – also common during Rewarming Phase
  - Vasodilation; may result in tachycardia and hypotension; requires tx

3. CV effects

- Cardiovascular (assuming pt deeply sedated and euvolemic)
  - ↑BP (MAP), ↑CVP, ↑M_V02
  - ↓HR
  - ↓CO (due to HR), but improved O_2 supply/demand ratio
    - Case series – cooling used for low cardiac output states (LCOS)
    - Used for JET post op ped cardiac patients

3. CV effects

- ECG changes –
  - Bradycardia (↓HR) common (↑PR, ↑ QRS,↑QT intervals)
  - No specific tx usually required for ↓HR, if temp >30ºC and otherwise stable
    - Atropine ineffective
    - If hypothermic without ↓HR, consider hypovolemia or inadequate sedation as cause
  - Other arrhythmias uncommon if temp > 30ºC!
  - Arrhythmias at temps < 30ºC
    - 28-30 ºC - ↑ (AF & VF)
    - < 28 ºC - ↑↑VF.
    - **STAT** and prompt rewarming to 33ºC required if ever <30ºC (MANUAL Mode required for Blanketrol-III)

4. Electrolytes (Potassium = K^+)

- Close monitoring of K^+ required post arrest due to AKI risk
- Electrolytes q 6 hr during cooling and rewarming phases and q 12 hr during other phases.
  - **Induction Phase** - serum K^+ <u>decreases</u>
    - Careful replacement as needed
  - **Rewarming Phase** - serum K^+ <u>increases</u>
    - Slow rewarming results in less elevation in K+
    - If patient received insulin for hyperglycemia and extra K^+ replacement given, this may result in greater ↑ K^+ on rewarming - - - be careful!
    - Consider removing K^+ from IV fluids during rewarming; supplement prn if needed

5. Hyperglycemia (GLU)

- Common post arrest due to stress response
- Relative insulin resistance with cooling
- Significance & optimal range for GLU unknown
- Neonatal, adult and THAPCA RCTs did not use tight control
- Often improves without tx in first 24 hr
- Important: if insulin for hyperglycemia used during cooling, will need more K^+ replacement. This may lead to HYPERkalemia and HYPOglycemia on rewarming as insulin resistance resolves.
- Protocol suggests <200 mg/dl (range 80-200) acceptable
  - consider reducing glucose in IV solutions, insulin only as needed for GLU > 200.
- Monitor q 6-12 hr. More often if insulin used.

6. Chemistries (other)

- 🡻 Phosphate, Magnesium, Calcium
  - Each may decrease during cooling
  - Monitored at least daily
  - Replace if indicated

7. LFTs, Amylase/Lipase, Lactate

- 🡹 Amylase, lipase, liver enzymes
- 🡹 Lactate (up to 6 mmol/L)
  - Monitor at least daily
  - No tx generally required
  - Elevations also commonly associated with cardiac arrest

8. Hematology/Coagulation

- Platelets
  - Mildly reduced numbers common
  - May require tx [platelet transfusion] if level too low for clinical setting (e.g., chest tube bleeding).
- Mild abnormalities coagulation studies ~ 33ºC
  - NOT seen when measured in lab (37ºC)
  - Usually requires no tx [FFP transfusion]
- Clinical trials including THAPCA-IH did not describe increased bleeding with cooling.
- Monitor at least daily

9. Hematologic (Neutropenia)/Infection

- ↓ WBC (neutropenia) may occur
- Impaired inflammatory response with cooling
- Potentially higher risk of infection
- Out of hospital cardiac arrests commonly associated with VAP and/or BSI in adults
- THAPCA overall positive cultures 39-46% (lung, blood and urine). Drowning subgroup 43-67%
- **IMPORTANT:**

  Consider antibiotic prophylaxis in BOTH cooled & normothermia groups as fever will be masked by TTM in both.

10. Drug Metabolism

- Drug clearance often dependent on enzyme reactions
- Hypothermia is expected to be associated with slower drug clearance and potentially higher drug levels (opiates, benzos, NMBs, etc.).
  - Follow levels if available (i.e. phenobarb)
  - Titrate sedation drugs to effect
  - Consider cautious use of drugs that cause bradycardia (i.e., dexmedetomidine?)

11. Metabolic Rate

- Reduced with cooling (32-34ºC)
  - ~8-10% per degree C
- Caloric requirements decrease during cooling
  - ~30-40%
- Do not over feed

12. Blood Gases

- P_aO_2 and P_aCO_2 solubility differs by temp
- A rough estimate of temp correction to 33ºC

  ~ P_aCO_2 = ↓2 torr/ºC = ~ 8 torr

  ~ P_aO_2 = ↓5 torr/ºC = ~20 torr
- Controversial if correction should be done
- P-ICECAP, like THAPCA, will not temp correct ABGs
- Report at standard body temp 37.0ºC

13. Skin

- Closely observe skin and provide good nursing care during 120 hrs. of temperature management.
  - Cooling not associated with skin break down in Neonatal cooling trials up to 72 hr. or THAPCA 48 hr.
- Larger, malnourished, immobile patients may be at greater risk

Central Temperature Measurement

Temperature Measurement

- Central temperature measurement required to estimate blood temp (Gold Standard)
- Delay in a central site to reflect blood temp in real time is associated with overshoot of cooling
  - Ideal site = accurate, short time lag
- Dual central temp measurements required for all patients (Primary to cooling device; Secondary to bedside monitor or cooling device).
- **Exception** - ECMO cases – 1 central temp (or venous circuit blood) only required

- **Esophageal** (Preferred primary site – attached to the cooling devise (Arctic Sun, Blanketrol, other). Used as sole temp site in NICHD neonatal trials
  - Accuracy: High level
  - Time lag: Shortest = 5 min (2-10 min)
  - Insertion: easy, but **MUST** verify position by CxR
  - IMPORTANT: Correct placement in lower 1/3 of esophagus is critical
    - If in stomach, temp may measure low by 1-3ºC
    - If tube feeds (gastric) and reflux, may make measurement inaccurate
    - Vented G-tube accuracy?
    - Position of ET tube in tracheal relative to probe location in esophagus
    - May move with neck extension/flexion

- **Rectal** (secondary probe– to monitor)
  - Accuracy: Moderate level
  - Time lag: Moderate = 15 min (10-40 min)
  - Insertion: Easy
  - Dislocation: Common. Monitor for it.
- **Bladder** (secondary probe – to monitor)
  - Accuracy: Moderate level
  - Time lag: Moderate = 20 min (10-60 min)
  - Insertion: Easy
  - Dislocation: Uncommon. Low urine output may result in less accurate measurements
  - Not available for smallest infants

*If Esophageal probe is not used as primary probe, then Rectal or Bladder will need to be selected.

- **Skin** sites (skin, axillary, etc)
  - Accuracy: Inaccurate – not a central temperature. Do not use.
  - Time lag: Moderate = 20 min (10-60 min)
  - Insertion: Easy
  - Dislocation: Uncommon
- **Tympanic** membrane (better than Skin)
  - Accuracy: Moderate, may be inaccurate
  - Time lag: Moderate = 10 min (10-20 min)
  - Insertion: Easy; quick
  - Dislocation: NA
  - Other: not continuously measured

Central Temp Differences

- Two central temps for safety
- If within ± 1ºC - acceptable
- If consistently > 1ºC, escalating action required
  - Notify the site PI
  - Verify probe placement (esophageal, rectal)
  - Verify YSI 400 compatible probes used
  - Stomach feeds/GE reflux (esophageal probe)
  - Low urine output (temp sensing Foley)
  - Determine which probe is most accurate to be Primary connected to the cooling device.
  - May need to check 3rd central temp site

Factors influencing ability to maintain goal temperature

1. Patient factors

- Patient factors impeding cooling
  - Size (larger, obesity)
  - Shivering (commonly subclinical)
    - Sedation/analgesia/NMB (Inadequate)
    - Sepsis/Infection
  - Seizures
  - Extremely reduced CO/poor skin perfusion
    - e.g. abdominal compartment syndrome.

2. Skin surface area for cooling

- Surface area (SA) for contact (Conduction)
  - 2 vs. 1 blankets (i.e., anterior/posterior vs. posterior)
  - Positioning of patient (i.e., side vs. back)
  - With Arctic Sun too few pads (surface area) may result in difficulty rewarming
- Extraneous materials between patient and blankets/pads (Maxi-Therm Lite blankets or Arctic Sun pads)
  - Minimize, none required, no sheets

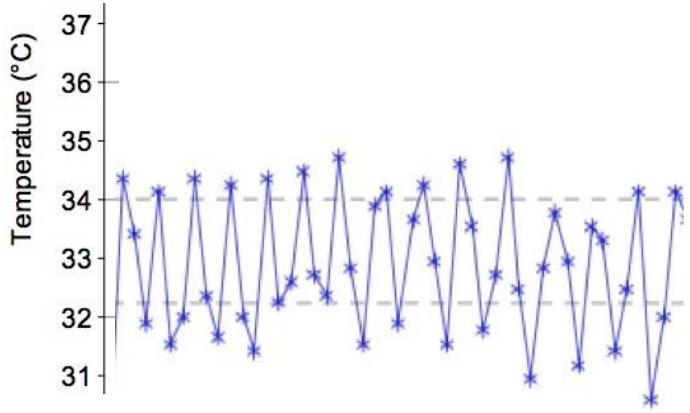
3. Cooling Devices

- Know how to use your site's cooling device/modes per the manufacturer's recommendations!
- Also, know important limitations of your device
- Most common devices used in P-ICECAP are:
  1) Blanketrol-III: Gentherm (formerly CSZ) has improved educational materials and videos on website.
     https://www.gentherm.com/en/medical/hyper-hypothermia/blanketrol-3
     https://gentherm.com/en/medical/resources-manuals/?section=blanketrol
     https://vimeo.com/403437211
  2) Arctic Sun: BD outstanding hands-on customer service
  3) Other (Criticool, etc.)
- Unlike THAPCA, we are not instructing on the use of any device. Examples used are for discussion purposes only. Call vendor for issues with temperature control.

3. Cooling Equipment: Example of modes – Blanketrol-III

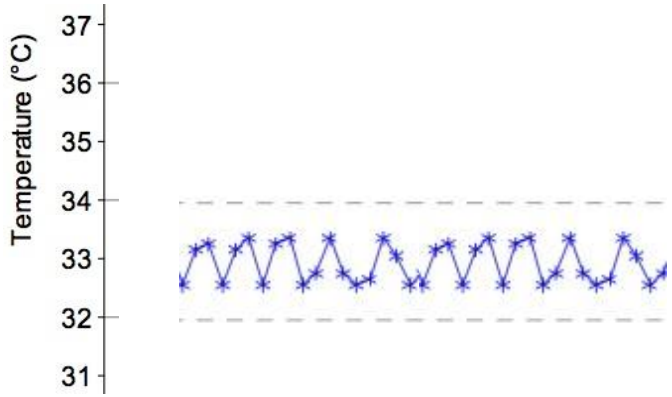
- **AUTO CONTROL Mode**
  - Warms or cools water to max range of 4 - 42ºC when patient's central temp +/- 0.2ºC from Blanketrol Set Point temp.
  - For large patients.
- **GRADIENT VARIABLE MODE (Plus SMART MODE)**
  - Cools water to narrower range; dampens temp fluctuation compared to AUTO CONTROL Mode.
  - For smaller patient sizes.
  - Example (assume patient 34ºC and set point 33ºC)
    - AUTO CONTROL: 4 - 42ºC For large patients
    - Gradient Variable 20ºC: 14 - 42ºC
    - Gradient Variable 10ºC: 24 - 42ºC. For smallest patients
- Defer to manufacturer/vendor for optimal set up and use

Temperature Tracings (from Primary Probe)



Not in range

- **AUTO Mode**
- **NMB, Sedation**



In range

- **GRADIENT VARIABLE Mode 10º C**
- **NMB, sedation**

3. Blanketrol and SMART MODE

- **GRADIENT VARIABLE with SMART MODE** – Blanketrol-III
- A modification to the GRADIENT VARIABLE MODE.
- SMART MODE will decrease the water temperature set in GRADIENT VARIABLE MODE by 5ºC if the goal temperature is not achieved within 30 minutes.
- It reverts to the GRADIENT VARIABLE MODE once the target temperature goal is achieved.
- This mode is suggested to be used by the manufacturer (Gentherm).

See User Guide and Inservice videos updated since THAPCA.

https://gentherm.com/wp-content/uploads/blanketrol-III-userguide-99217.pdf

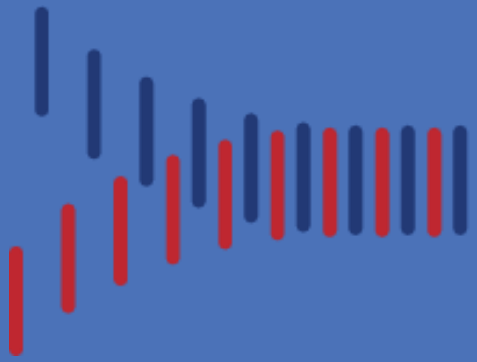
3. Blanketrol-III

- **Manual Mode** – Blanketrol-III
  - **Not** used except for emergencies
  - IMPORTANT: Key fact to know for Blanketrol! Manual mode is required if patient's (pt) temp is ever ≤**30ºC**.
    - None of the other Blanketrol Modes function if patient temp is ≤30ºC.
    - Suggest setting the Manual Mode to highest (warmest) setting (42ºC) briefly until the pt temp is 33ºC. Then use Auto Control or a Gradient Variable SMART Mode depending on patient size.

*IMPORTANT – in a Manual Mode there is no safety of servo control. The bedside nurse must continuously observe the pt's temp and adjust water temp. The pt is 100% dependent on temp titration by nurse.

Temperature Monitoring and Management

P-ICECAP



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HYPER-HYPOTHERMIA

Blanketrol® III

Patient Temperature Management Solutions

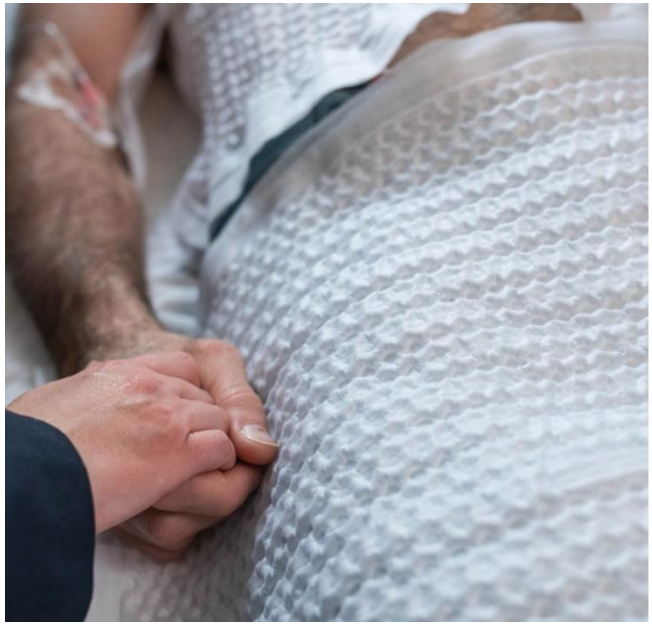
The Blanketrol® III hyper-hypothermia system offe
regulation while still keeping control in the hands o
program minimizes fluctuations in water temperatu
temperature.

Request More Information

Blanketrol® III Quick Reference Guide

Blanketrol® III User Guide

Blanketrol® III Inservice Video



HYPER-HYPOTHERMIA

Maxi-Therm® Lite Blankets

Single-Use Hyper-Hypothermia Blankets

Gentherm's Maxi-Therm® Lite hyper-hypothermia blankets have a strong bonded pattern in the blanket resulting in a long lasting seal during usage.

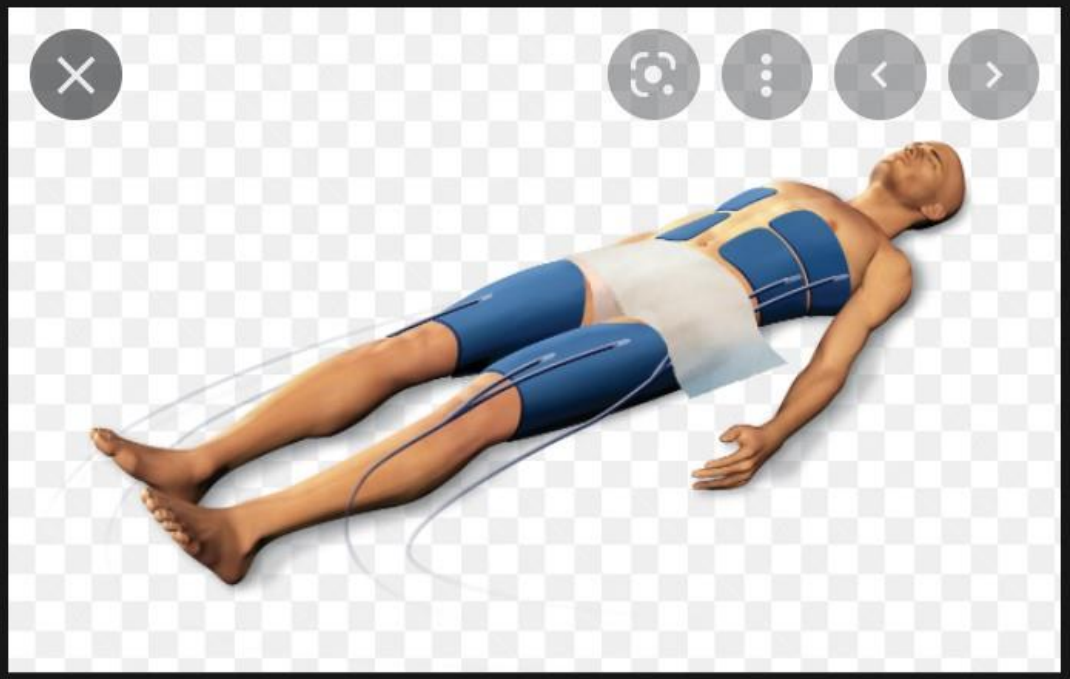
The white material provides a comfortable, clean feel, and in today's hospitals where hospital acquired infections are an important issue, having a white blanket helps notify the caregiver when the blanket is soiled and needs to be changed.

Request More Information

Yumpu

Arctic SunÂ®5000

Visit



BD

ArcticGel™ Pad Kit, Medium, 1 per case - 31707 | BD

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Neonatology Intensive Care Trauma & Emergency

Targeted Temperature Management Has Never Been Easier

Operating CritiCool is simple, with quick and easy setup, and is both user- and patient-friendly. Clinicians just have to:

- **Set the desired temperature on the CritiCool device**
- **Wrap the appropriately sized CureWrap garment around the patient**
- **Cool the patient to the set temperature**
- **Rewarm the patient through controlled, monitored rewarming**

Belmont Medical Technologies

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Criticool MINI: Battery Hypothermia Cooling Machine | Belmont Medical

CONNECT WITH US

One machine.
One system.

A. Three water circuits

Simple, self-sealing hose ports eliminate water spillage and maximize performance, efficiency, and speed to target temperature. All three water circuits can be individually monitored for ease of use.

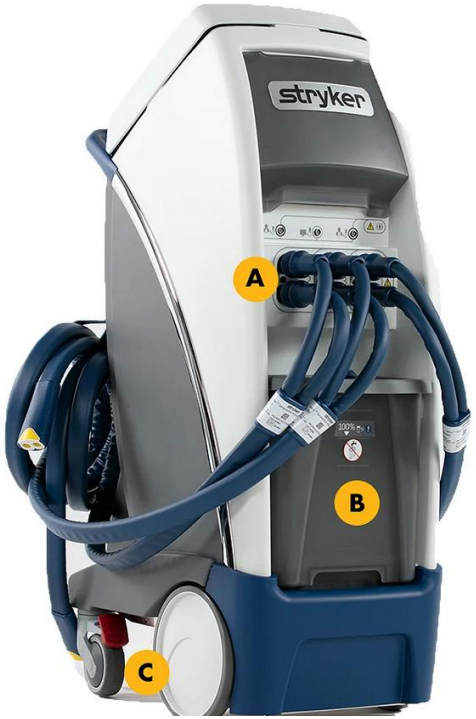
B. Removable water reservoir

Therapy setup is simple and easy, and allows for uninterrupted temperature management while adding or refilling water with the translucent, removable water reservoir

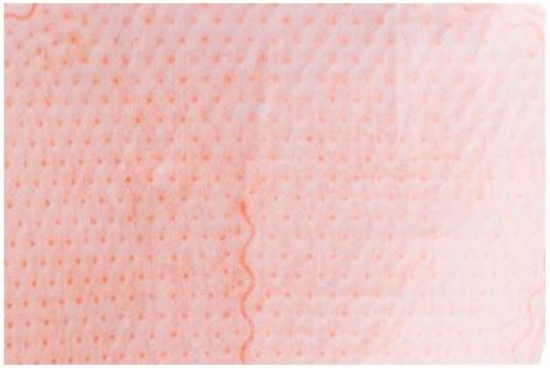
C. Ease of mobility

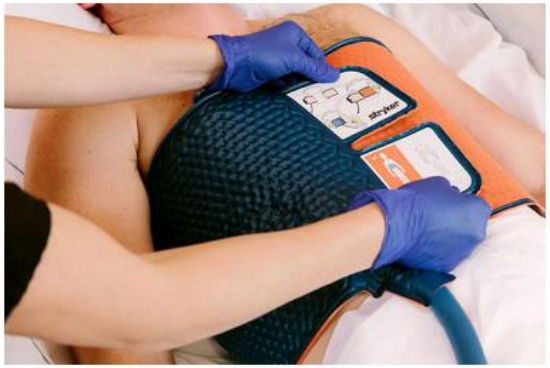
Altrix was designed with ergonomic support in mind. This usability, alongside its proven durable features, results in one machine that can easily be maneuvered throughout the entire hospital.

TALK WITH A REP



Altrix Temperature Management Wraps





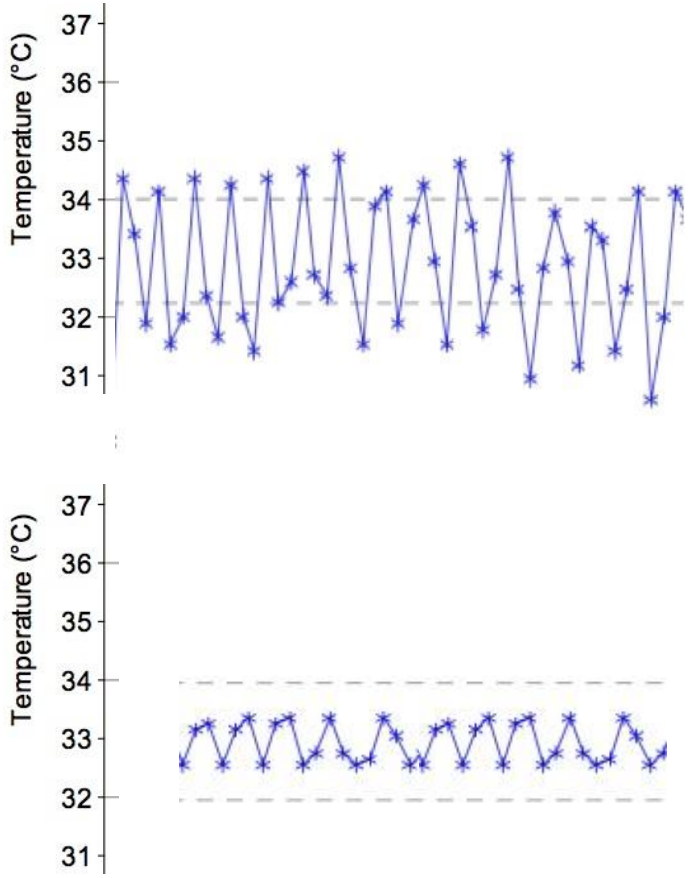
Monitoring: TTM 33°C (32-34°C)

- Two central temperature probes.
  - Primary to cooling device (Blanketrol-III, Arctic Sun, other).
    - *This temperature is entered into the case report form (CRF).
  - Secondary to bedside monitor or device (safety).

Monitoring: TTM 33°C (32-34°C)

- Initial cooling device's target temp is 33°C (range 32-34°C) until rewarming. (Exception 0 hr cooling/ normothermia group).
- Different devices have different settings/modes for small to large sized patients.
  - If temp is not staying in the 32-34°C range, you need to adjust cooling device per manufacture (e.g., next slide).
    - Arctic Sun (excellent hands-on support)
    - Blanketrol-III (good online instructions & videos)
    - Both have 24/7 hotline numbers for support.
  - The on-call P-ICECAP team has 24/7 hotline that is available for other study questions.

Temperature tracings from small child (primary probe)



Not in 32-34ºC range: Overshooting

- **B-3, AUTO Mode**
- **NMB, Sedation**
- **Water temp ~4 to 42ºC**

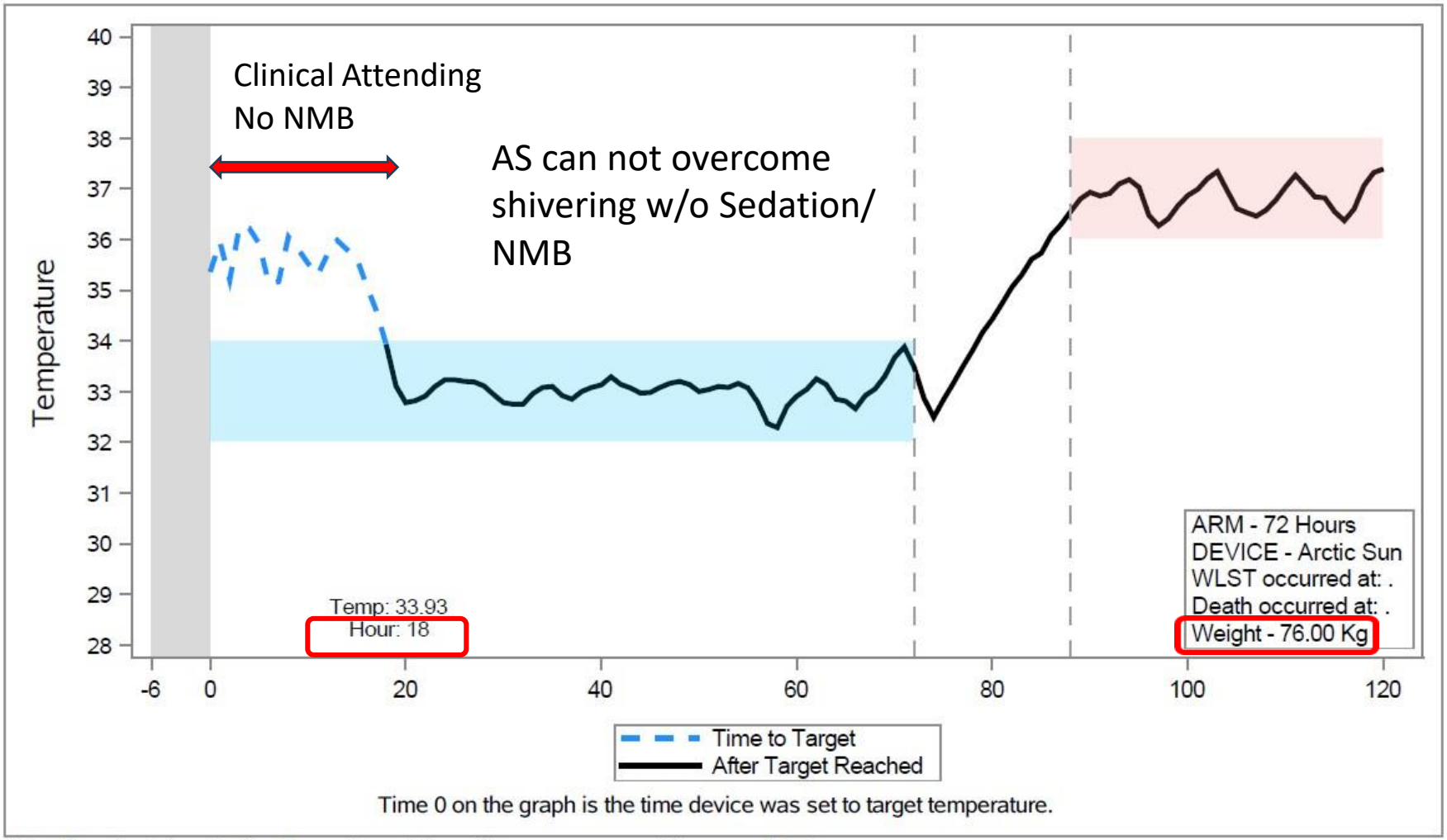
In range

- **B-3, Changed to GRADIENT VARIABLE 10ºC Mode**
- **NMB, sedation**
- **Water temp ~23 to 42ºC**

Temperature Management

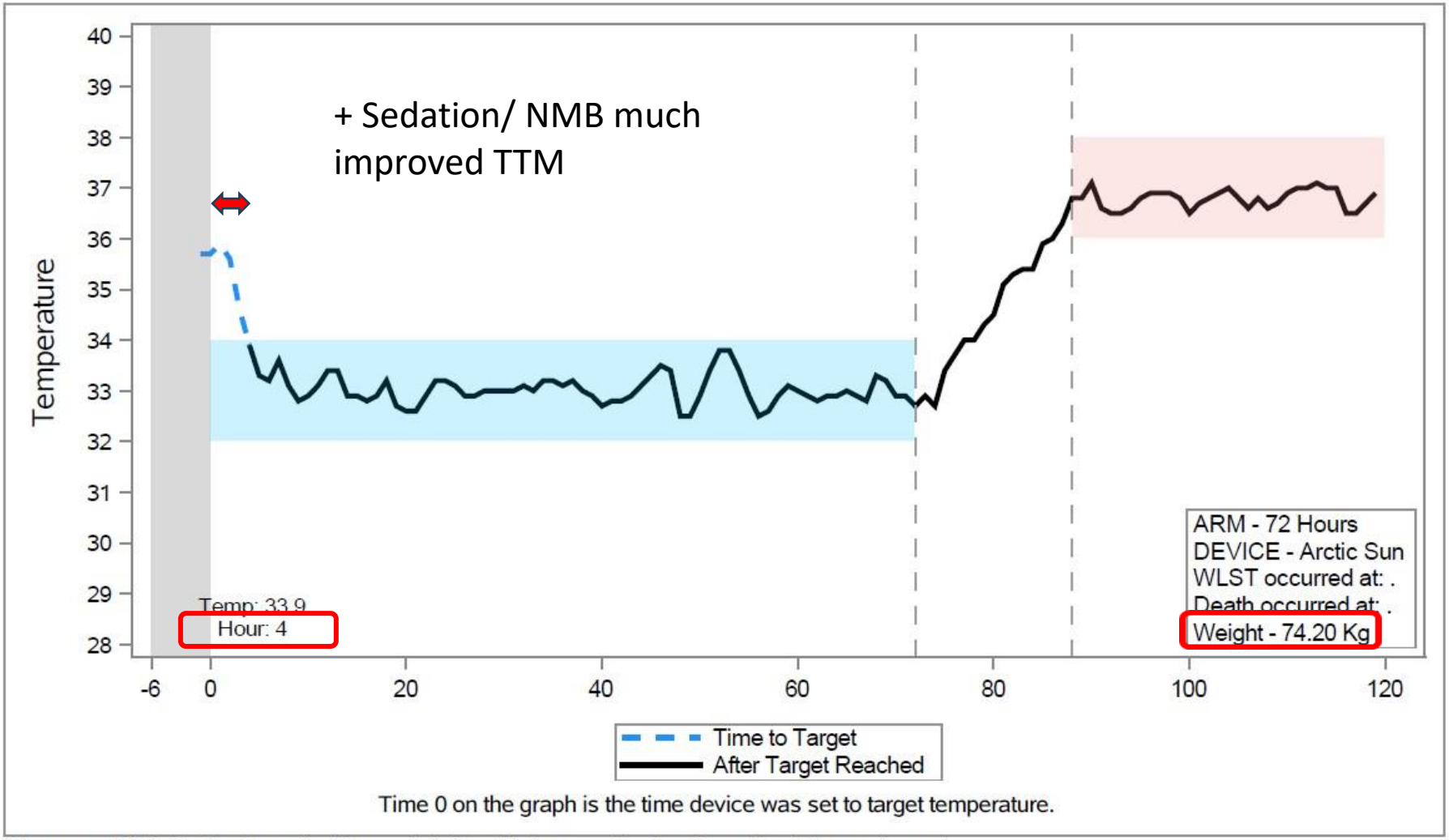
- A major goal in P-ICECAP is to achieve the desired phase target temperatures for the 120-hour intervention while **preventing** shivering.
- Sedation and analgesia are generally used throughout the120 hours while a patient remains intubated.
- Use NMB for Induction and Rewarming phases. Other times PRN. **MUST** avoid shivering. (examples)
- Subclinical shivering is common. In patients with difficult to maintain temperature, consider additional sedation with NMB trial.

Subject 1115



Attending physician declined use of paralytic until neuro exam could be completed.
Rewarming was delayed slightly by the delivery of acetaminophen at 1628.

Subject 1104



3 hours and 15 minutes for patient to reach below 34 degrees C- obesity and took longer to cool

Protocol Overview Through 120 Hours

P-ICECAP

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Overview – from 37,000 feet

- Example – University of Michigan
- PICU fellow is contacted re: an OHCA from outside ED or our UM ED.
- The research team on call is immediately notified of a pending OHCA admit.
- Research team discusses with clinical team the case summary, arrival time, and approach for consent
- Order for nursing to get cooling equipment to bedside:
  - Blanketrol-III, two Maxi-Therm Lite cooling blankets (Ped or Adult), 2 hoses, 2 temperature probes and temp sensing Foley of correct size
- On pt arrival, clinical team stabilizes, places CVC, art line.
- Cooling device started as soon as it is safe to set up.
- Clinical team initiates their usual TTM target between 33-37ºC before consent.

Overview – from 37,000 feet

- Research team introduced by clinical team to family. Then gets informed consent and randomizes to one of 10 cooling durations from 0 to 96 hours.
- Subject enrollment = time randomized to a study cooling duration.
- TTM 33°C (or 36.8°C for 0 cooling normothermia group) will be set as target temp no later than 15 min after randomization.
  - If it was started prior to randomization, then the start time for cooling groups 12-96 hr will be when a target 32-34°C set.
  - For normothermia 0 hr cool group, start time is when site begins toward a target of 36-37.5°C.
- Protocol goal is to achieve a temp range no later than 2 hr. after randomization.
  - Sedation and NMB for induction phase results in fastest time to goal
  - *Ideally, research team supervises until temp stable

Overview – from 37,000 feet

- Cooling duration is equal to the combined time of the Induction plus Maintenance phases.
- For nine cooling groups (12-96 hr), after the assigned cooling duration is completed, slow rewarming over at least 16 hrs.
- Then normothermia 36.8°C for rest of 120 hr.
- Exception is the 0 hour controlled normothermia group. The pt brought to 36.8 °C ASAP, then normothermia for remaining 120 hr.

P-ICECAP Trial: Cooling, Rewarming and Normothermia Phases

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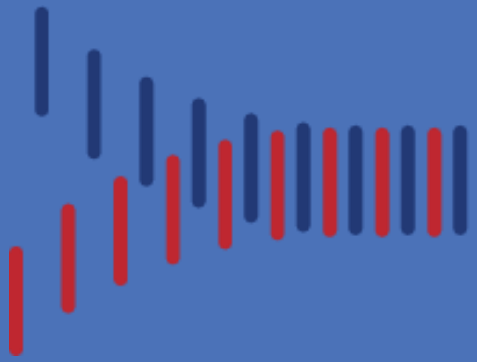

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Cooling Groups: 12, 18, 24, 36, 48, 60, 72, 84, 96 hours

Cooling Groups: 12, 18, 24, 36, 48, 60, 72, 84, 96 hours

Induction Phase (I)

- Time from start of TTM 33ºC (or 32-34ºC if pre randomization) until the goal range (32-34ºC) is reached.
- Use the recommended cooling modes described by manufactures for the patient's size.
  - Blanketrol III - AUTO CONTROL or GRADIENT VARIABLE SMART MODE – per manufacturer.
  - Arctic Sun – per manufacturer.
- Induction will require sedation + analgesia and NMB
  - **MUST PREVENT SHIVERING!**
- Likely time of maximum BP instability following OHCA since closest to event
- Hypovolemia, Hypokalemia and Hyperglycemia may occur during this period
- 'Just in time' review with clinical team optimal

Cooling Groups: 12, 18, 24, 36, 48, 60, 72, 84, 96 hours

Maintenance Phase (II)

- Steady state period with target temperature 33ºC (32-34ºC) until assigned study cooling duration is completed and planned rewarming starts.
- Adjust the cooling device mode as needed per manufacturer to keep in the goal 32-34ºC range.
- Titrate sedation/analgesia to achieve/maintain "sluggish or no response to noxious stimulus."
- NMB prn after stable 32-34ºC temp range is achieved.
- Similar clinical issues as Induction Phase possible (Hypovolemia, Hypokalemia and Hyperglycemia).

Cooling Groups: 12, 18, 24, 36, 48, 60, 72, 84, 96 hours

Rewarming Phase (III)

- This is a critical time – it needs to be done slowly.
- Begins with the initiation of planned increase of device target temp toward 36.8ºC (normothermia) goal.
- Should be done over ≥ 16 hrs
- For Blanketrol-III: AUTO CONTROL or GRADIENT VARIABLE SMART MODE
  - Manually **Increase** temp set goal 0.7 ºC every 4 hrs.
    - **33ºC** (0 hr); **33.7ºC** (0-4hr); **34.4ºC** (4-8hr); **35.1ºC** (8-12hr); **35.8ºC** (12-16hr); then **36.8ºC** (16+hr)
  - Goal temp of 36.8ºC (36-37.5ºC range) after 16 hrs
- For Arctic Sun – the rate of rewarming is programed to achieve the goal of 36.8ºC (from 33ºC) over 16-18 hr.

Cooling Groups: 12, 18, 24, 36, 48, 60, 72, 84, 96 hours

Rewarming Phase (III)

- BP, Potassium, and Glucose need to be monitored carefully during rewarming.
- Electrolytes and glucose at least every 6 hrs. and more frequently if indicated.
- Increased sedation and NMB is usually required as the shivering response increases with rewarming
- Fluid bolus often needed.
- Rapid rewarming must be avoided to minimize risks of cerebral edema, hypotension, hyperkalemia and hypoglycemia.
- Review issues of the Rewarming Phase with the clinical team prior to its start.
- Call the 247 on-call number if any questions.

Cooling Groups: 12, 18, 24, 36, 48, 60, 72, 84, 96 hours

Normothermia Phase (IV)

- Goal temp is 36.8°C, range 36-37.5°C for remaining time to 120 hrs
- If clinical team determines they must check fever status, put in MONITOR ONLY Mode
- Return to the device's appropriate cooling mode if temp > 37.5°C, but only if the patient remains intubated. Sedation/analgesia and possibly NMB may be required to prevent shivering

Cooling Groups: 12, 18, 24, 36, 48, 60, 72, 84, 96 hours

Normothermia Phase (IV)

- Clinical team may elect to extubate patient if clinically awake and otherwise stable
  - Management of fever following extubation is limited to antipyretic agents (Tylenol). Will NOT be able to use the cooling device with deep sedate or NMB to prevent shivering.
  - Can use temp MONITOR Only Mode

*IMPORTANT: Do NOT extubate a patient until rewarmed! Cerebral edema, hypoglycemia, hyperkalemia, and hypotension are risks of rapid rewarming.

Controlled Normothermia = Zero (0) Hours of Additional Cooling Group

Controlled Normothermia = Zero (0) Hours of Additional Cooling Group

- This arm is effectively TTM 36.8°C for 120 hrs
- Temp will be maintained through 120 hrs from when the cooling device is set with the intent to establish normothermia
  - either to a set temp $\geq$ 36°C OR
  - otherwise beginning active rewarming with the intent to establish normothermia in children who are hypothermic
- Set temp to 36.8°C within 15 minutes of randomization if appropriate

Controlled Normothermia = Zero (0) Hours of Additional Cooling Group

- Pts will be rewarmed promptly per routine clinical practice, and will not be rewarmed using the 16 hr procedure for the arms that receive therapeutic hypothermia for 12 to 96 hours.
- Reasonable ranges of rewarming can range from 0.5- 1°C per hr or more.
- Pts should be rewarmed as fast as tolerated to achieve normothermia. (In THAPCA trials, the normothermia group was set to achieve 36.8°C ASAP).
- If the pt's temp is < 32°C, the pt should be rewarmed ASAP to 33°C for safety to minimize the risk of arrhythmia.

Controlled Normothermia = Zero (0) Hours of Additional Cooling Group

- If a pt is hyperthermic (>37.5°C) at randomization?
  - The device should be set at 36.8°C to cool to normothermia range (36-37.5°C) ASAP

Initial Site Enrollments

- For the first 2 patients enrolled at each site, we recommend you contact the on-call **247 P-ICECAP hotline 844-742-3227 (844-PICECAP)** to review the Induction Phase soon after device is set to 33°C. Call again just prior to start of the Rewarming Phase.
- The other time to call is for a site's 1st randomization to normothermia (0 hr cooling) group
- Since sites are using their own cooling devices, we are relying on sites and manufacturers to use their cooling equipment safely. Contact your vendor for an in-service if you believe it would benefit your PICU/PCCM team.
- Arctic Sun may have already contacted you.
- Contact Gentherm (Blanketrol) and other manufactures as needed for in-services.

Questions?

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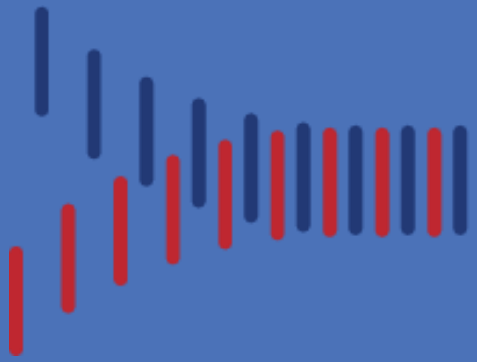

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