



Therapeutic Hypothermia After Cardiac Arrest: Best Practices 2014

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Advanced Life Support: 2010 International Consensus on Cardiopulmonary Resuscitation and Emergency Cardiovascular Care Science With Treatment Recommendations

- Comatose adult patients (not responding in a meaningful way to verbal commands) with spontaneous circulation after out-of-hospital cardiac arrest should be cooled to 32°-34°C for 12-24 hours.
- Induced hypothermia might benefit comatose adult patients with spontaneous circulation after out-of-hospital cardiac arrest from a nonshockable rhythm or cardiac arrest in hospital.
- TH is recommended in combination with primary PCI, and should be started as early as possible, preferably before initiation of PCI

Pathophysiology

- During cardiac arrest, neurological deficits result from ↓cerebral oxygen delivery due to ↓BP/lack of perfusion
- Hypoxic brain causes cerebral edema and failure of synaptic transmissions
- Reperfusion can exacerbate cerebral edema, initiate destructive chemical cascades, and alter the inflammatory response with further tissue injury
- Result is compromised neurological function after successful resuscitation from a cardiac event

Effects of Therapeutic Hypothermia

- Cooling the patient for 24 hours and slowly rewarming limits the effects of cerebral hypoxia and reperfusion
- Hypothermia slows cerebral metabolism (\downarrow O₂ consumption by 6% for each degree in body temperature reduction)
- Hypothermia limits cerebral cell death and lessens cerebral edema

What We Know and Do Not Know

- Benefits in witnessed cardiac arrest when initial rhythm pulseless VT or Vfib (best outcomes)
- Benefits in nonshockable rhythm (PEA or asystole) and in-hospital cardiac arrest (consider)
- Optimal time after return of spontaneous circulation (ROSC) to start TH (sooner the better)
- Optimal temperature (32°- 36°C)
- Optimal method (intravascular vs surface)
- Optimal duration of TH (24 – 48 hours)
- How fast to rewarm (slowly)
- Optimal neurological outcomes (evolving)

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- **Optimal neurological outcomes (evolving)**

Inclusion Criteria

- Adult >18 years
- Witnessed out-of-hospital cardiac arrest when initial rhythm pulseless VT or Vfib; consider in PEA or asystole; consider after in-hospital cardiac arrest
- ROSC within 60 minutes from start of CPR
- Unconscious with GCS < 8 after ROSC
- Endotracheal intubation with mechanical ventilation
- Initial temperature > 30°C

Exclusion Criteria

- Patients who were comatose prior to cardiac arrest (head injury, drug overdose, status epilepticus, suspected intracranial hemorrhage)
- Uncontrolled GI bleeding
- Patients who are terminally ill/DNR order
- Patient not intubated
- Rapidly improving neurological status
- Temperature $< 30^{\circ}\text{C}$ after cardiac arrest
- MAP < 60 mmHg despite fluids and vasopressors
- ***Variability continues in who receives TH***

Camp-Rogers TR, et al. An observational study of patient selection criteria for post-cardiac arrest therapeutic hypothermia. [Review]. Resuscitation 2013;84:1536-9.

Therapeutic Hypothermia Phases

- Rapidly cool the body core to target temperature
- Maintain target temperature for 24 hours
- Slowly rewarm (0.25 – 0.5°C/hour)



What is the Optimal Time after ROSC to Start Therapeutic Hypothermia?

- The sooner the better as delays in inducing TH may lead to poorer neurologic outcomes
- Pre-hospital induction of TH reduces time to goal temperature when compared to cooling after hospital admission
- Is it safe and advantageous for Emergency Medical Service (EMS) personnel to begin TH immediately post resuscitation in the pre-hospital setting?

Sendelbach S, et al. Effects of variation in temperature management on cerebral performance category scores in patients who receive therapeutic hypothermia post cardiac arrest. *Resuscitation*. 2012;83:829-34.

Cabanas JG, et al. Field-induced therapeutic hypothermia for neuroprotection after out-of hospital cardiac arrest: a systemic review of the literature. *J Emerg Med*. 2011.40(4):400-9.

Inclusion Criteria

- No guidelines currently exist for initiation and maintenance of pre-hospital TH after out of hospital cardiac arrest (OHCA)
- Minimum standards that should be considered:
 - ROSC after OHCA not related to blunt or penetrating trauma or hemorrhage
 - No purposeful response to pain
 - Patient will be transferred to a hospital capable of continuing TH

Wallace SK and Abella BS. Pre-hospital therapeutic hypothermia. In Lundbye JB (Ed.) Therapeutic hypothermia after cardiac arrest. Springer, New York. 2012.

Challenges

- Incomplete neurological assessment
- Pre-hospital TH performed by EMS may result in longer transport times (additional task)
- Cost of equipment and training of EMS personnel
- EMS personnel must have access to accurate methods to monitor temperature when inducing TH in pre-hospital setting
- Tympanic thermometer devices easy to use, but less reliable than esophageal, bladder, or rectal temperature
- Risk of unintentional overcooling ($<33^{\circ}\text{C}$)

Induction Methods

- Rapid intravenous infusion of large volume cold (4°C) crystalloid solution (30 mL/kg up to 2 liters)
- Surface cooling or ice packs
- Combination of both

Cold Intravenous Fluids

- 30 to 40 mL/kg cooled to 4°C infused over 30 min reduces core temperature 2°C - 2.5°C
- Decreases time to therapeutic temperature (32 - 34°C)
- Simple, safe, inexpensive, and effective in lowering body temperature
- Patient continues to cool after rate decreased (overshoot goal temperature)
- Small studies suggest no improvement in outcome at hospital discharge compared with cooling in the hospital

Bernard SA, et al. Induction of therapeutic hypothermia by paramedics after resuscitation from out-of hospital ventricular fibrillation cardiac arrest: a randomized controlled trial. *Circulation* 2010;122:737-42.

Bernard SA, et al. Induction of prehospital therapeutic hypothermia after resuscitation from nonventricular fibrillation cardiac arrest. *Crit Care Med* 2012;40:747-53.

Virkkunen I, Yli-Hankala A, Silfvast T. Induction of therapeutic hypothermia after cardiac arrest in prehospital patients using ice-cold ringer's solution: a pilot study. *Resuscitation*. 2004. 62:299-302.

Does Cold Intravenous Fluids in Pre-Hospital Setting Improve Outcomes?

- **1359 patients** randomized to prehospital infusion of up to 2L at 4°C NS following ROSC or standard care
- 583 patients presented with VF; survival to discharge 62.5% in the intervention group vs 64.3% in control group, p=0.69
- 776 patients presented with non-VF; survival to discharge was 19.2% in the intervention group vs 16.3% in control group, p=0.3
- No improvement in survival among patients resuscitated from out of hospital VF or non-VF; data does not support routine initiation of cooling using cold fluid in pre-hospital setting
- Recent review (2014) of randomized trial data demonstrates no important patient benefit from prehospital initiation of TH.

Kim F, Nichol G, Maynard C, et al. Effect of prehospital induction of mild hypothermia on survival and neurological status among adults with cardiac arrest: a randomized clinical trial. *JAMA* 2014 Jan 1;311(1):45-52.

Hunter BR, et al. No benefit to prehospital initiation of therapeutic hypothermia in out-of-hospital cardiac arrest: a systematic review and meta-analysis [Review]. *Academic Emergency Medicine* 2014. 21:355-64.

Regional System of Cardiac Resuscitation

- Significant improvements in outcome have been seen in regionalization of care
- Requires coordinated actions between EMS personnel, emergency medicine physicians, cardiologists, critical care physicians, neurologists, nurses, respiratory therapists, pharmacists, and others
- Requires protocol-driven decisions to match patient needs with capability of the destination hospital
- Requires effective communication from EMS to hospitals to mobilize personnel and equipment before arrival and reduce time delays to treatment

Facilitating Process: EMS Communication/Documentation

- Time and ECG rhythm on arrival
- Time person found unresponsive
- Actions performed (CPR, shock, medications)
- Duration of CPR
- Time of ROSC and GSC (no response to pain)
- Temperature measurement and device used
- Cooling initiated and type (per protocol)
- Time of transfer
- Time of arrival at ED

The NEW ENGLAND JOURNAL of MEDICINE

ORIGINAL ARTICLE

Nov 2013

Targeted Temperature Management at 33°C versus 36°C after Cardiac Arrest

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for the TTM Trial Investigators*



TTM-trial – 2010-2013

- 950 patients randomized
- 36 hospitals
- 10 countries
- Europe and Australia



Funded by:

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AFA-insurance Foundation, Sweden

Swedish Research Council

Governmental and Regional funding within the Swedish National Health System

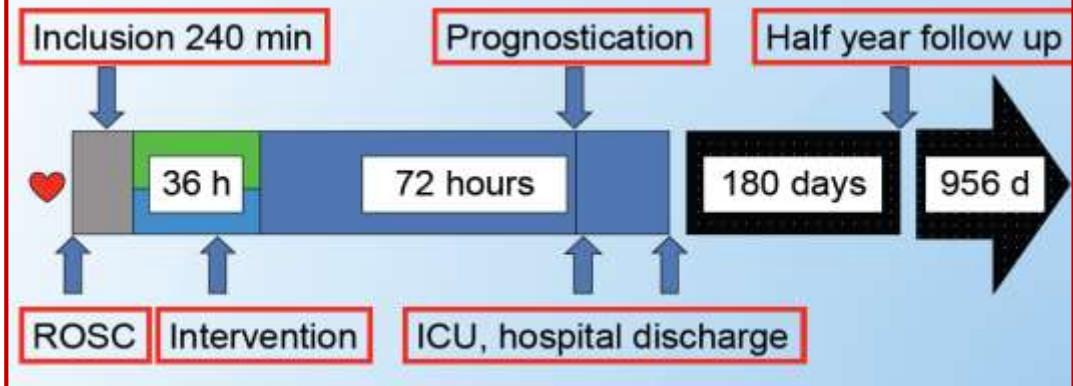
TrygFoundation, Denmark

Zoega, Krapperup, Thure Carlsson, Trolle-Wachtmeister foundations, Sweden



Design and timeline

- All patients sedated minimum 36 hours
- Feed-back controlled cooling devices in all patients
- Intravascular or surface devices



Baseline characteristics

	33°C	36°C
No.	473	466
Age	64+/-12	64+/-13
Male sex	83 %	79 %
Arrest in place of residence	52 %	55 %
Arrest in public place	42 %	40 %
Bystander witnessed	89 %	90 %
Bystander CPR	73 %	73 %
Shockable rhythm	79 %	81 %
Arrest to ROSC (min)	25 [18-40]	25 [16-40]
Circulatory shock	15 %	14 %
Lactate mmol/L	6.7±4.5	6.7±4.5
ST-elevation infarction	40 %	42 %
GCS	3 [3-4]	3 [3-4]

Outcome	TTM33	TTM36	HR or RR (95% CI)	P Value
PRIMARY OUTCOME				
Mortality at the end of trial				100% follow-up
Dead no./total no. (%)	235/473 (50)	225/466 (48)	HR=1.06 (0.89-1.28)	0.51
SECONDARY OUTCOMES				
Neurological function at follow-up				99% follow-up
CPC 3-5--no./total no. (%)	252/469 (54)	242/464 (52)	RR=1.03 (0.91-1.16)	0.88
mRS 4-6--no./total no. (%)	245/469 (52)	239/464 (52)	RR=1.01 (0.89-1.14)	0.87
Serious adverse events				
Any event--no./total no. (%)	439/472 (93)	417/464 (90)	RR=1.03 (1.00-1.08)	0.09

Glasgow-Pittsburgh Cerebral Performance Categories (CPC) Scale

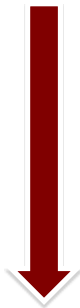
- CPC 1 Full recovery
- CPC 2 Moderate disability
- CPC 3 Severe neurologic disability but preserved consciousness
- CPC 4 Comatose
- CPC 5 Death

Degree of post-arrest injury

severe

moderate

Mild / none



**Poor outcome
with any TTM**

**Good outcome
with any TTM**

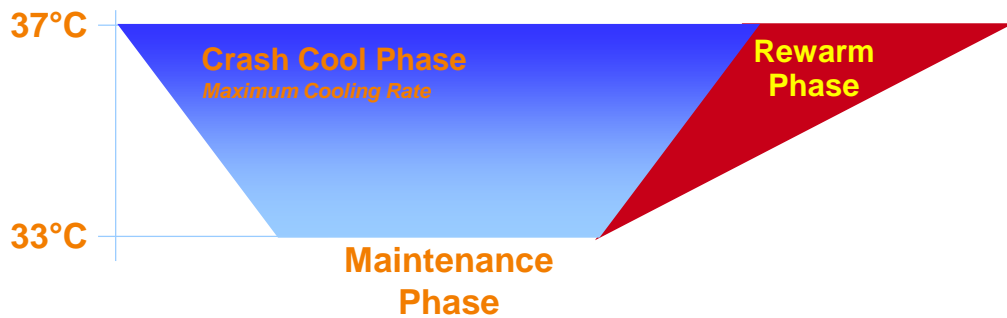
**dose of TTM
(33°C v 36°C, e.g.)
affects outcome**

Recommendations – Ben Abella, MD, University of Pennsylvania

- It is reasonable to not change current practice based on the TTM trial, but rather continue to treat comatose post-arrest patients with a TTM goal temperature of 33°C.
- However, the TTM trial provides evidence that a more flexible approach is possible – for patients intolerant of 33°C (marked bradycardia, increased bleeding, marked QT prolongation) or for patients that clinicians feel uncomfortable with treating to 33°C for other clinical factors, it is acceptable to treat with higher TTM temperature goals, up to 36°C.

Choosing the Cooling Device

- Rapidly cools the body core to target temperature
- System automatically and precisely maintains target temperature
- Easy-to-use, multi-functional
- “Hands free” operation reduces nursing time
- Improved access to patient



Tight control for 24 hours

Non-Invasive

- Ice packs to neck, groin, and axillae
- 30 to 40 mL/kg cold (4°C) crystalloid infusion
- Cooling blankets or mats
- Automated surface cooling devices

Cooling Blankets or Mats

- Manual system with reusable vinyl water blankets
- Placed under and/or over patient
- Air trapped between blanket and patient acts as insulator, resulting in slow thermal transfer
- Challenges
 - Coverage impedes patient care
 - No feedback loop making temperature maintenance difficult with high incidence of overcooling
 - Skin erythema, mottling, breakdown from hypothermic skin vasoconstriction

Automated Surface Cooling Devices

- Arctic Sun (Bard)
- Medi-Therm III (Gaymar)
- KoolKit (Cincinnati Subzero Products)
- ThermoWrap (MTRE Advanced Technologies)
- EMCOOLS Pads (Emcools)

Arctic Sun

- Automated temperature control system that provides rapid, precise control for inducing hypothermia and rewarming
- Adhesive, hydrogel energy transfer pads (conductive heat transfer)
- Temperature controlled water circulates through the pads in response to patient temperature and a preset target temperature
- Pads cover 40% BSA (back, abdomen, thighs)
- Cooling rate of 1.2°C per hour
- Continuous temperature reading through foley catheter with temperature probe



Invasive/Intravascular

- Thermogard XP® System/Zoll Alsius CoolGard 3000
- InnerCool RTx Endovascular System (Philips)

ZOLL Intravascular Temperature Management (IVTM™)

- Automated temperature control system that provides rapid, precise control for inducing hypothermia and rewarming
- Cooling device and central venous catheter
- NS circulates through a balloon catheter with a textured surface located in the vena cava
- Venous blood cooled by direct contact with catheter
- Goal temperature achieved in 2-3 hours
- Continuous temperature reading through foley catheter with temperature probe

ZOLL Intravascular Temperature Management (IVTM™)

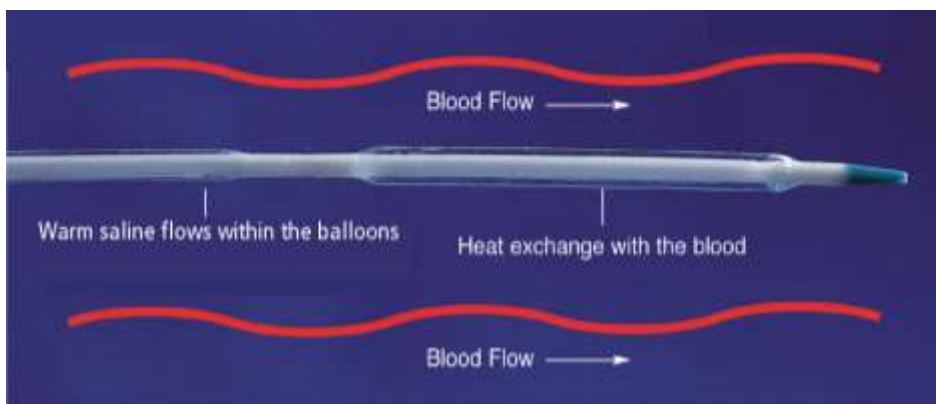
Console controls cooling and re-warming (Thermogard XP®)

Catheter placement options:

- Femoral
- Subclavian
- Internal jugular

Catheters provide triple-lumen central venous access





- Cool or warm saline flows within the balloons
- Blood is cooled or warmed as it passes by each balloon
- Closed-loop system – no fluid infusion to the patient

Invasive vs Noninvasive

- Zoll Alsius CoolGard 3000 vs Medivance Arctic Sun
- 167 comatose cardiac arrest patients
- Same postresuscitation treatment protocol
- No difference in survival with good neurologic function at discharge or 12 months
- Time of arrest to achieving TH was equal
- More hyperglycemia with Arctic Sun
- More hypomagnesemia with Zoll Alsius

Tomte O, et al. A comparison of intravascular and surface cooling techniques in comatose cardiac arrest survivors. Crit Care Med 2011; 39:443-9.

Adverse Effects of Therapeutic Hypothermia

- Suppresses ischemia-induced inflammatory reactions that occur after cardiac arrest with ↑risk of infection (changes in WBC function)
- Mild bleeding
- Mild acidosis and ↑lactate occurs (trending)
- Diuresis resulting in metabolic and electrolyte disorders (hyperglycemia; K⁺, Mg⁺, Ca⁺⁺ and phosphorus loss)
- Shivering (↑O₂ consumption)
- Bradycardia
- Reduced drug metabolism

Infection

- Pneumonia common in unconscious patients after cardiac arrest
- Sepsis rare but more frequent in patients with intravascular cooling or with coronary angiography
- Pneumonia and sepsis have not been associated with ↑mortality

Nielson N, et al. Adverse events and their relation to mortality in out-of-hospital cardiac arrest patients treated with therapeutic hypothermia. *Crit Care Med* 2011;39:57-64.

Pinchon N. Efficacy of and tolerance to mild induced hypothermia after out-of-hospital cardiac arrest using an endovascular cooling system. *Crit Care* 2007;11:R71.

Geurts M, et al. Therapeutic hypothermia and the risk of infection: A systematic review and meta-analysis. *Crit Care Med* 2014;42:231-42.

Shivering

- Natural defense against hypothermia to generate heat
- Impedes the process of inducing or maintaining TH
- Shivering ↑ metabolic rate that may worsen cell injury
- During TH induction, shivering occurs 34°-36°C, but then diminishes when temperature <34°C

Bedside Shivering Assessment Scale (BSAS)

Score	Definition
0	None: no shivering noted of the masseter, neck or chest wall
1	Mild; shivering localized to neck and/or thorax only
2	Moderate; shivering involves gross movement of upper extremities (in addition to neck and thorax)
3	Severe; shivering involves gross movements of trunk and upper and lower extremities

Badjatia N ,et al. Metabolic impact of shivering during therapeutic temperature modulation: the bedside shivering assessment scale. *Stroke* 2008;39:3242-7.

Management of Shivering

- Prevent shivering (continuous infusion) vs as needed (prn dosing)
- Meperidine (50 mg IV q 6 hrs)
- Buspirone (30 mg po q 8 hrs)
- Deep sedation (midazolam, fentanyl, propofol, lorazepam)
- Neuromuscular blockade (vecuronium 0.1 mg/kg bolus; cisatracurium infusion 0.15 mg/kg bolus followed by 1-10 mcg/kg/min infusion)
- NMB could mask seizure activity but can help achieve goal temperature faster

Seizures

- Incidence 3 – 44% after ROSC
- May be refractory to medications
- No studies addressing prompt and aggressive treatment after the first seizure after ROSC
- No difference in the occurrence of seizures after ROSC in patients treated with TH or without TH

Neurologic Outcomes

- Poor neurologic outcomes associated with
 - First rhythm at cardiac arrest not Vfib/Vtach
 - Acute kidney injury in ICU
 - GCS < 8 at 12 hrs after rewarming

Vanston VJ, et al. Predictors of poor neurologic outcome in patients undergoing therapeutic hypothermia after cardiac arrest. South Med J 2010;103:301-6.

Neurologic Prognostication - Evolving

- Clinical examination
 - EEG
 - Biomarkers
 - Neuroimaging
-
- No single test can predict poor prognosis with absolute certainty, however specificity of clinical exam and SSEP improves when performed beyond 72 hours

Golan E, et al. Predicting neurologic outcome after targeted temperature management for cardiac arrest: systematic review and meta-analysis. Crit Care Med 2014. 42:1919-30.

Clinical Examination

- Absence of brain stem reflexes, motor response, and presence of myoclonus (neuro clinical exam) 72 hours after cardiac arrest has been considered an adequate predictor of poor prognosis after TH
- “The prognosis is invariably poor in comatose patients with absent pupillary or corneal reflexes, or absent or extensor motor responses three days after cardiac arrest” (AAN, 2009)

AAN. Prediction of outcome in comatose survivors after cardiopulmonary resuscitation. AAN. 2009.

Fugate JE, et al. Predictors of neurologic outcome in hypothermia after cardiac arrest. Annals of Neurology 2010;68:907-14.

Greer DM, et al. Clinical examination for prognostication in comatose cardiac arrest patients. Resuscitation 2013; 84:1546-51.

Somatosensory Evoked Potentials (SSEP)

- EEG monitoring
- Cortical N20 response measured after electrical stimulation of median nerve
- Bilateral absence of N20 response between 24-48 hours after CA accurately predicts poor prognosis in patients who have not undergone TH
- N20 response prolonged but present in patients who have undergone TH; studies do support bilateral absence of N20 predict poor prognosis
- However, there is one instance in literature where one patient had bilateral absence of N20 response 72 hours after TH induction and rewarming and achieved normal cognitive function

Leithner C., et al. Does hypothermia influence the predictive value of bilateral absent N20 after cardiac arrest. *Neurology*. 2010;74:965-9.

EEG Monitoring

- With TH after CA, EEG patterns are usually low voltage with seizure activity
- NMB can mask seizure activity
- Seizures should be treated if found on EEG
- EEG cannot predict outcome (an initial flat EEG has no prognostic value), but helpful in identifying patterns
- Standard intermittent EEG has comparable performance with continuous EEG both for variables important for outcome prognostication

Rundgren M, et al. Continuous amplitude-integrated electroencephalogram predicts outcome in hypothermia-treated cardiac arrest patients. *Crit Care Med* 2010;38:1838-44

Blondin N, et al. Neurologic prognosis in cardiac arrest patients treated with therapeutic hypothermia. *The Neurologist* 2011;17:241-248

Alvarez V, et al. Yield of intermittent versus continuous EEG in comatose survivors of cardiac arrest treated with hypothermia. *Critical Care (London, England)* 2013;17:R190.

Neuron Specific Enolase (NSE)

- NSE is a protein contained in neurons that is released in anoxic brain injury
- Effective in determining neurologic outcome after cardiac arrest.
- Recently studied in patients treated with TH after cardiac arrest (CA)
- NSE values were lower in patients with better neurological outcomes, however the absolute cut-off value that can be used to predict poor outcomes is not yet known.

- “ Serum NSE levels > 33 ug/L at days 1 to 3 post-CPR accurately predict poor outcome“.
- Newer reports of patient’s regaining consciousness despite NSE levels >100 ug/L
- NSE levels are attenuated by hypothermia; delayed testing may be necessary
- Laboratory variations can be significant

Prediction of outcome in comatose survivors after cardiopulmonary resuscitation. AAN. 2009.

Neuroimaging

- Neuroimaging is an evolving modality as a prognostic parameter in cardiac arrest survivors
- CT, MRI
- Positron emission tomography, single photon emission computed tomography
- Quality of the available literature is not robust
- Need for higher quality studies before neuroimaging can be supported as a standard tool for prognostication in the patient population.

Hahn D. Quality of evidence in studies evaluating neuroimaging for neurologic prognostication in adult patients resuscitated from cardiac arrest. [Review]Resuscitation 2014. 85:165-72.

Fever After Rewarming

- Fever associated with poor neurologic outcome after stroke and trauma; suspected in patients treated with TH after CA
- Avoid fever after target temperature reached
- Acetaminophen every 6 hours prn unless there is evidence of liver dysfunction
- Maintain external or internal temperature management devices to maintain temperature 37°C

Cocchi MN. Fever after rewarming: incidence of pyrexia in postcardiac arrest patient who have undergone mild therapeutic hypothermia. *Journal of Intensive Care Medicine* (2014);29(6):365-9.



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