UTAH SOCIETY OF
HEALTH-SYSTEM PHARMACISTS

Resident Fall CE Series
November 12, 2020

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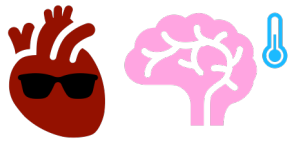
Keeping It Cool in Post-Cardiac Arrest Patients



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University of Utah Health
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PollEverywhere Audience Response

- ACPE requires active learning and most prefer real-time participation rather than a graded post-test
- We are utilizing PollEverywhere software for this process.
- You may join to participate by 3 different ways:
  - **Web Browser: Go to PollEv.com/ushp**
  - **PollEverywhere app: Download app and join ushp presentation**
  - **Text Messaging: Text ushp to 22333**
- We recommend the PollEverywhere app or web browser as they are easier to respond
- For each question, you can click on the correct answer in Web Browser or App or text correct answer to 22333

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Disclosure

- Relevant Financial Conflicts of Interest
  - CE Presenter, Helen Hou
    - none
  - CE mentor, Cole Sloan
    - none
- Off-Label Uses of Medications
  - Propofol, ketamine, magnesium sulfate, buspirone, meperidine, dexmedetomidine, fentanyl, midazolam, dantrolene, ondansetron, tramadol, clonidine, vecuronium, cisatracurium

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Learning Objectives

- Pharmacist Objectives:
  - Recognize the benefits and adverse effects of targeted temperature management
  - Select the most appropriate pharmacological interventions to manage shivering during targeted temperature management
  - Compare the evidence and outcomes between lower versus higher temperature targets (33ºC versus 36ºC)
- Technician Objectives:
  - Describe the physiologic effects of hypothermia and hyperthermia in post-cardiac arrest patients
  - Identify medications used during the different phases of targeted temperature management
  - Examine how to prioritize safe and efficient delivery of medications for patients receiving targeted temperature management

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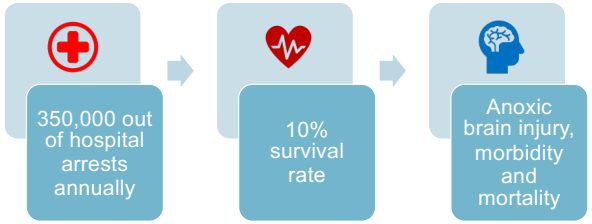
Background



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Khera R et al. Hospital variation in the utilization and implementation of targeted temperature management in out-of-hospital cardiac arrest. Circulation: Cardiovascular Quality and Outcomes. 2018 Nov;11(11):e004829.

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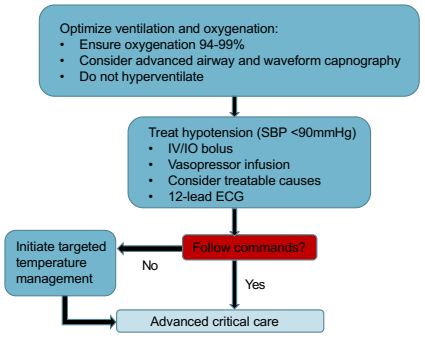
Post-Cardiac Arrest Care: American Heart Association (AHA)



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American Heart Association. 2019 AHA Focused Update on ACLS. AHA/ASA Journals. 2019;140(24): e881-e894

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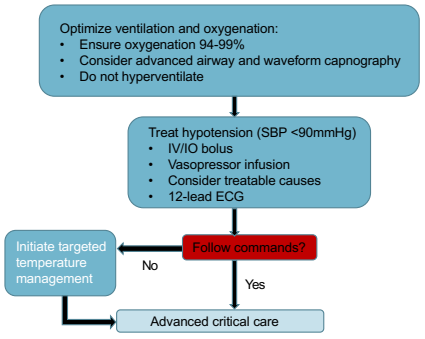

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American Heart Association. 2019 AHA Focused Update on ACLS. AHA/ASA Journals. 2019;140(24): e881-e894

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Overview of Targeted Temperature Management (TTM)

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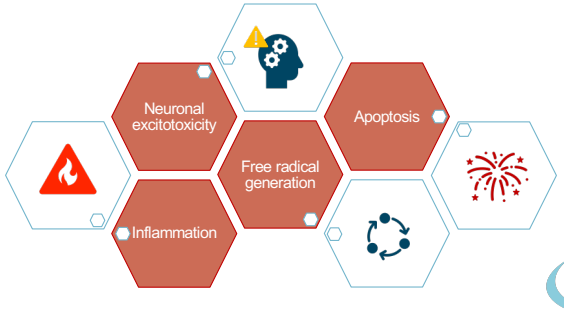
Hyperthermia Post-Cardiac Arrest



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2. Dietrich, W. D., & Bramlett, H. M. (2007). Hyperthermia and central nervous system injury. Progress in Brain Research, 162, 201-217.
3. Zeiner, A et al. (2001). Hyperthermia after cardiac arrest is associated with an unfavorable neurologic outcome. Archives of internal medicine, 161(16), 2007-2012.

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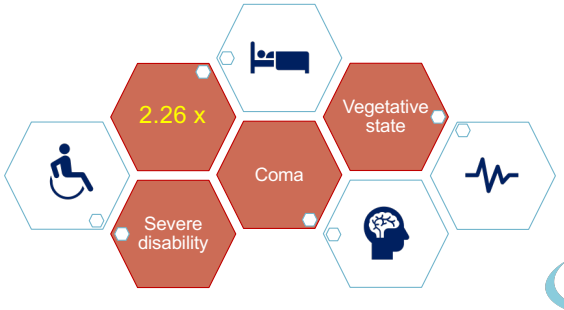
Hyperthermia Post-Cardiac Arrest



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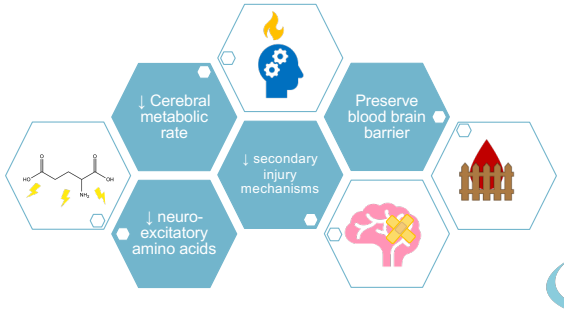
Physiologic Benefits of Hypothermia



Kamatovskaia, L. V., Wartenberg, K. E., & Freeman, W. D. (2014). Therapeutic hypothermia for neuroprotection: history, mechanisms, risks, and clinical applications. *The Neurohospitalist*, 4(3), 153-163.

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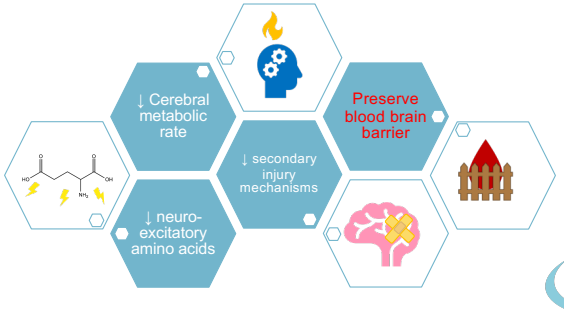
Physiologic Benefits of Hypothermia



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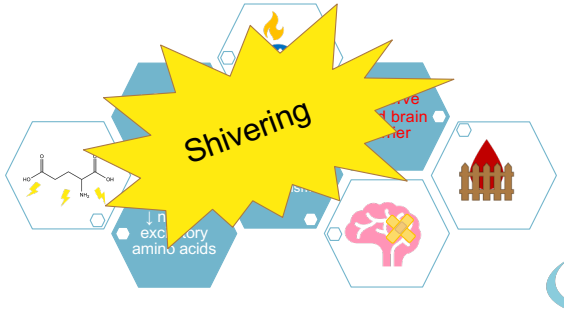
Complication
~~Physiologic Benefits~~ of Hypothermia



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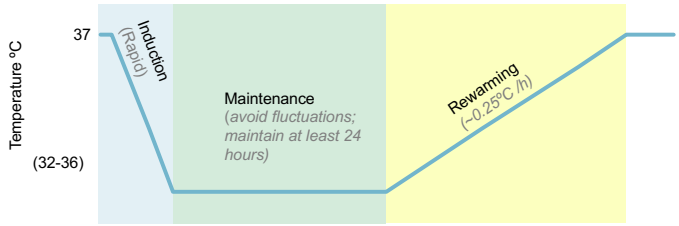
Phases of TTM



1. Bindra, A., & Gupta, D. (2016). Targeted temperature management in neurocritical care: Boon or bust. *Journal of Neuroanaesthesiology and Critical Care*, 3(02), 096-109.
2. Perman, S. M., Goyal, M., Neumar, R. W., Topjian, A. A., & Gaieski, D. F. (2014). Clinical applications of targeted temperature management. Chest, 145(2), 386-393.

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Tools for TTM

Non-invasive	Invasive
Air/water circulated cooling blankets	Intravascular catheters
Ice packs	Infusion of ice-cold Lactated Ringer's
Water/alcohol sprays	Extracorporeal circulation
Skin exposure	Antipyretics
Immersion in cold water	

Bindra, A., & Gupta, D. (2016). Targeted temperature management in neurocritical care: Boon or bust. *Journal of Neuroanaesthesiology and Critical Care*, 3(02), 096-109.

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2015 AHA Post Cardiac Arrest Guideline Recommendations

- Recommend TTM over no TTM in adults with out of hospital cardiac arrest
- Select and maintain constant target temperature between 32 - 36ºC
- Cool for at least 24 hours
- Recommend AGAINST use of pre-hospital cooling

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Actual Application of TTM

- Wide practice deviations from guidelines
- Decreased TTM use overtime
  - Misinterpretation of studies
    - Controversy over outcomes from different temperature targets
  - Limited experience from providers
    - 1-2 times/year

Khera R, Humbert A, Leraux B, Nichol G, Kudenchuk P, Scales D, Baker A, Austin M, Newgard CD, Radecki R, Vilke GM. Hospital variation in the utilization and implementation of targeted temperature management in out-of-hospital cardiac arrest. Circulation: Cardiovascular Quality and Outcomes. 2018 Nov;11(11):e004829.

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Patients undergoing targeted temperature management post-cardiac arrest are recommended by AHA to be cooled to:

A. 30ºC
B. 32-36ºC
C. 25-30ºC
D. All of the above
E. None of the above

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Effects and Complications of TTM

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Physiologic Changes in TTM

Cardio	Renal	Electrolytes	Immune system	Endocrine	Heme

• ↓ Heart rate
• ↓ Cardiac output
• ↑ Blood pressure
	• Hypovolemia	• Cooling:
		  • HypoK+
		  • HypoMg+
		  • HypoPhos
		• Rewarming:
		  • HyperK+
			• Infection risk	• Cooling:
				  • Hyper-glycemia
				• Rewarming:
				  • Hypo-glycemia
					• ↓ Platelet function
					• ↓ White blood cells
					• Impaired coagulation

1. Omairi AM, Pandey S. Targeted Temperature Management (TTM, Therapeutic Hypothermia). InStatPearls [Internet] 2020 Mar 5. StatPearls Publishing.
2. Saigal S, Sharma JP, Dhurwe R, Kumar S, Gurjar M. Targeted temperature management: current evidence and practices in critical care. Indian journal of critical care medicine: peer-reviewed, official publication of Indian Society of Critical Care Medicine. 2015 Sep;19(9):537.

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Which of the following is an expected physiologic change during the initial cooling phase of targeted temperature management?

A. Bradycardia
B. Leukocytosis
C. Hypotension
D. Hypervolemia

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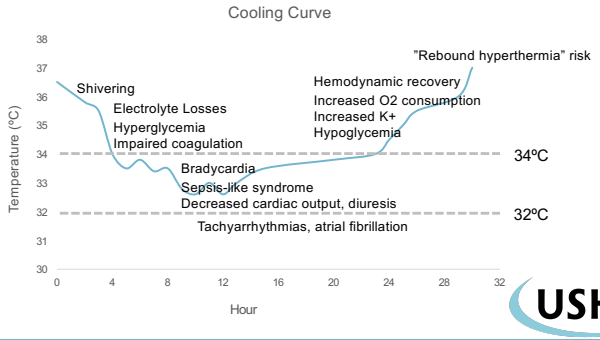
Complications of TTM



Perman SM, Goyal M, Neumar RW, Topjian AA, Gaieski DF. Clinical applications of targeted temperature management. Chest. 2014 Feb 1;145(2):386-93.

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What are two common physiologic effects of targeted temperature management should we monitor for during the rewarming phase?

I. Hypokalemia
II. Hyperkalemia
III. Hypoglycemia
IV. Hyperglycemia

A. I & III
B. II & III
C. I & IV
D. II & IV

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Electrolyte and Glucose Shifts

- Cooling:
  - ↓ insulin sensitivity and secretion → ↑ blood glucose → ↑ insulin requirement
  - K+ shifts inside cell → ↓ K+ → ↑ K+ supplementation
- Rewarming:
  - Rebound ↑K+
    - Cautiously supplement during rewarming
  - ↓ blood glucose
    - Check glucose frequently and cautiously give insulin

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Scaravilli V, Bonacina D, Citerio G. Rewarming: facts and myths from the systemic perspective. InCritical care 2012 Jun 1 (Vol. 16, No. S2, p. A25). BioMed Central.

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True or false: during the cooling phase of targeted temperature management, you may expect that a patient will require higher doses of insulin compared to the rewarming phase:

A. True
B. False

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Goals of pharmacological therapies

- ↓ Adverse electrolyte/ metabolic effects of hypothermia
- ↓ Shivering threshold and shivering
- ↑ Patient comfort and sedation

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Shivering Management

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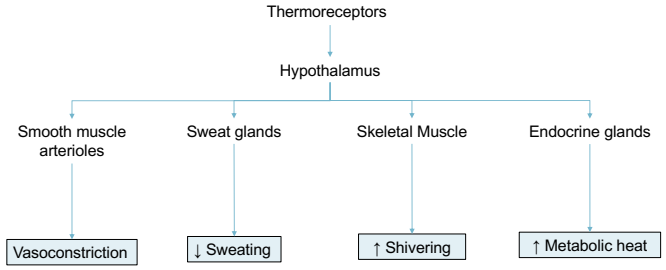
Physiology of Thermoregulation



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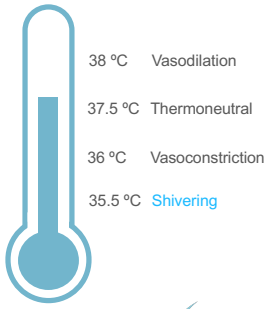
Shivering

- Increases heat production up to 600%
- Triples oxygen consumption
- Prolongs induction (cooling) time



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Bedside Shivering Assessment Scale

Score	Shivering	Behavior
0	None	No shivering
1	Mild	Shivering localized to neck/ thorax, may be seen only as artifact on ECG or palpitation
2	Moderate	Intermittent involvement of upper extremities +/- thorax
3	Severe	Generalized shivering or sustained upper/lower extremity shivering

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Therapies for Shivering

- Approaches:
  - Lower shivering threshold
    - Buspirone
    - Meperidine
    - Dexmedetomidine
    - Opioids
  - Vasodilation; reduce smooth muscle tone
    - Magnesium
  - Paralysis
    - Neuromuscular blockers

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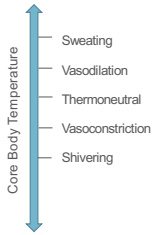
Therapies for Shivering

Medication	Mechanism	Benefits
Buspirone	5-HT1A partial agonist (*Use with meperidine or dexmedetomidine)*	Minimal toxicities (sedation, dizziness, nausea)
Meperidine	κ-opioid and α_2 receptor agonist → Decrease oxygen consumption and catecholamine excretion (*Monotherapy or with buspirone/ dexmedetomidine)*	Effective in lowering shivering threshold
Dexmedetomidine	α_2 agonist	No respiratory depression for waking subjects
Magnesium	NMDA antagonist, calcium antagonist → peripheral vasodilation	Possible neuroprotection



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1. Weant KA, Martin JE, Humphries RL, Cook AM. Pharmacologic options for reducing the shivering response to therapeutic hypothermia. Pharmacotherapy: The Journal of Human Pharmacology and Drug Therapy. 2010 Aug;30(8):830-41.
2. Orhan-Sungur M, Komatsu R, Lenhardt R. Buspirone and dexmedetomidine synergistically reduce the shivering threshold in humans. Anesthesiology. 2006 Oct 17;105:A1224

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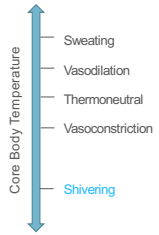

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A 50 year old male presents to your hospital with an out-of-hospital cardiac arrest with a shockable rhythm. After achieving ROSC, the team decides to initiate targeted temperature management. Which of the following medication will you NOT recommend as a 1st option to prevent shivering?

A. Acetaminophen
B. Meperidine + Buspirone
C. Cisatracurium
D. Dexmedetomidine
E. Magnesium sulfate

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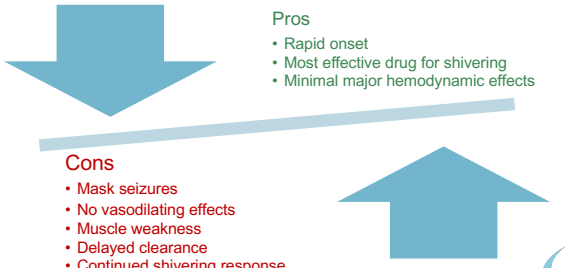
Therapies for Shivering: Paralytics



Pros
- Rapid onset
- Most effective drug for shivering
- Minimal major hemodynamic effects

Cons
- Mask seizures
- No vasodilating effects
- Muscle weakness
- Delayed clearance
- Continued shivering response

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Polderman KH. Application of therapeutic hypothermia in the intensive care unit. Intensive care medicine. 2004 May 1;30(5):757-69.

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Patient Comfort: Sedation and Analgesia

- Goals:
  - Optimize regimen before paralysis
  - Use lowest dose with shortest half-life

Medications	Mechanism	Pros	Cons
Fentanyl	Opioid analgesic	Fast onset, potent	Respiratory depression, chest wall rigidity, ileus, decreased clearance during hypothermia
Propofol	Sedative, suppress excitatory neurotransmitter	Fast onset and offset, decrease shivering threshold	Hypotension, bradycardia, propofol infusion syndrome, hypertriglyceridemia

Weant KA, Martin JE, Humphries RL, Cook AM. Pharmacologic options for reducing the shivering response to therapeutic hypothermia. Pharmacotherapy. The Journal of Human Pharmacology and Drug Therapy. 2010 Aug;30(8):830-41.

Hypothermia's effects on drug metabolism

Medication	Body temperature (°C)	Effect
Fentanyl	32	↑ [Plasma] 25%
Propofol	34	↑ [Plasma] 28%
Rocuronium	30.4	↓ Clearance to 51%
Vecuronium	< 35, 35-35.9, 36-36.9	↓ Clearance 11.3% per degree
Midazolam	35.5-36.5	↓ Clearance 11% per degree

Zhou J, Poloyac SM. The effect of therapeutic hypothermia on drug metabolism and response: cellular mechanisms to organ function. Expert opinion on drug metabolism & toxicology. 2011 Jul 1;7(7):803-16.

Operational Considerations

Medication Safety Considerations

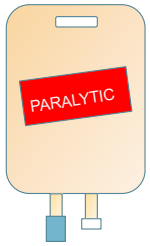
- Sound-Alike:
  - BusPIRone vs buPROPion
  - Demerol (brand meperidine) vs Dilaudid
  - Ketamine vs ketorolac
  - DexMEDEtomidine vs dexAMETHasone
  - Precedex (brand dexmedetomidine) vs Peridex (brand chlorhexidine)
  - Vecuronium vs valproate, vancomycin
- Look-Alike:
  - Propofol vs liposomal bupivacaine (both milky white)

Preparation of Paralytics

- Compounding:
  - Concentrations of vials

Drug	Vial concentrations	Diluted concentrations
Rocuronium	10 mg/mL	Up to 5 mg/mL
Vecuronium (powder)	Reconstituted to 1 mg/mL (10 mg, 20 mg sizes)	100-200 mcg/mL
Cisatracurium	2 mg/mL, 10 mg/mL	400 mcg/mL

- Risk of errors
- Labeling



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Storage

	Beyond use date		
Drug (in original vials)	Rocuronium	Vecuronium	Cisatracurium
Usual storage for manufacturer exp	Refrigerated	Room temp	Refrigerated
Room temp	60 days	Manufacturer exp	21 days
Diluted vials with NS, D5W, LR	24 hours (room temp)	24 hours (refrigerated)	24 hours (room temp or refrigerated)

- Segregate and differentiate paralytics!

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Delivery

- Prioritizing
  - Can't tube paralytics
  - Deliver to more "urgent" locations first
- Paralytics– safety considerations
  - Pay attention to location: OR, ED, ICUs
  - In-person hand-off
  - Don't leave it lying around!
  - Labeling: "WARNING: PARALYING AGENT– CAUSES RESPIRATORY ARREST"

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Shortage Concerns

- Propofol
- Midazolam
- Rocuronium
- Vecuronium
- Cisatracurium
- Ketamine
- Fentanyl

ASHP Current Drug Shortages [database on the Internet]. Bethesda (MD): American Society of Health-System Pharmacists: 2020; [updated Aug 2020; cited 30 Aug 2020]. Available from: https://www.ashp.org/Drug-Shortages/
FDA Drug Shortages [database on the Internet]. Silver Spring (MD): U.S. Food and Drug Administration: 2020; [updated Aug 2020; cited 30 Aug 2020]. Available from: https://www.accessdata.fda.gov/scripts/drugshortages/

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An ICU nurse sends a message to the technician requesting for a first dose of continuous cisatracurium STAT for a shivering post-arrest patient. Which of the following options represent the most safe and efficient delivery of this medication?

A. Tube cisatracurium to the ICU floor since it's STAT
B. Ask the runner to deliver it immediately; if unable to find the nurse, leave it outside of the patient cassettes so the nurses will see it first
C. Ask the nurse to do bedside compounding since it's most efficient way to initiate the medication STAT
D. Prepare the IV bag with appropriate warning labels and ask the runner to deliver the medication immediately to the ICU first

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How Low Should We Go?
Literature Review of Trials

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TTM Guideline Recommendations

2013 ACC/AHA STEMI	• 32 – 34ºC • (LOE B)
2015 AHA Post Cardiac Arrest Care	• 32 - 36ºC • (Class 1, LOE B)
2016 Canadian Cardiovascular Society-Optimal Post-Arrest Care	• 32 - 36ºC • (Strong recommendation)
2017 AAN Reducing Brain Injury After Cardiopulmonary Arrest	• 32- 34ºC (Level A) • 36ºC (Level B)

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Abbreviations: AAN = American Academy of Neurology; ACC = American College of Cardiology; AHA = American Heart Association; LOE = level of evidence; STEMI = ST Elevation Myocardial Infarction

Major Studies

- HACA (2002)
- Bernard et al (2002)
- Nielsen et al (2013)
- HYPERION (2019)

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HACA (2002): Design

Objectives
- Determine targeted temperature 32-34ºC vs normothermia after cardiac arrest led to a difference in neurologic outcomes within 6 months or differences in mortality

Design
- Multicenter, randomized controlled trial

Population
- N = 275, ventricular fibrillation or ventricular tachyarrhythmia (shockable)

Intervention
- Treatment group: within 4 hours after ROSC, cooled to 32-34ºC for 24 hours

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Hypothermia after Cardiac Arrest Study Group. Mild therapeutic hypothermia to improve the neurologic outcome after cardiac arrest. New England Journal of Medicine. 2002 Feb 21;346(8):549-56.

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HACA (2002): Conclusions

Conclusion
- More patients in hypothermia group (55%) vs normothermia group (39%) had favorable neurologic outcomes within 6 months (RR 1.4, P = 0.009)
- Fewer incidences of death in hypothermia group (41%) vs normothermia group (55%) (RR 0.74, P = 0.02)

Limitations
- Control group had Tmax > 37ºC
- No coma severity data pre-randomization

Takeaway
- Post-cardiac arrest patients should be cooled to 32-34ºC for 24 hours to improve outcomes and decrease mortality

USHP

Hypothermia after Cardiac Arrest Study Group. Mild therapeutic hypothermia to improve the neurologic outcome after cardiac arrest. New England Journal of Medicine. 2002 Feb 21;346(8):549-56.

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Bernard et al (2002): Design

Objectives
- Determine if moderate hypothermia 33ºC vs normothermia led to differences in hospital survival to discharge or neurologic function

Methods
- Randomized, controlled trial

Population
- N = 77, ventricular fibrillation out of hospital arrest (shockable)

Intervention
- Treatment group: within 2 hours of ROSC, cooled to 33ºC and actively rewarmed at 18 hours for 6 hours

USHP

Bernard SA, Gray TW, Buist MD, Jones BM, Silvester W, Gutteridge G, Smith K. Treatment of comatose survivors of out-of-hospital cardiac arrest with induced hypothermia. New England journal of medicine. 2002 Feb 21;346(8):557-63.

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Bernard et al (2002): Conclusions

Conclusions
- Better neurologic outcomes in hypothermia (49%) vs normothermia (26%) group
- No difference in mortality or adverse events (ex., significant cardiac arrhythmias)

Limitations
- Unable to blind physicians
- Potential exclusion of patients with poor prognosis

Takeaways
- Post-cardiac arrest, patients should be cooled to 33ºC to improve neurologic outcomes

USHP

Bernard SA, Gray TW, Buist MD, Jones BM, Silvester W, Gutteridge G, Smith K. Treatment of comatose survivors of out-of-hospital cardiac arrest with induced hypothermia. New England journal of medicine. 2002 Feb 21;346(8):557-63.

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HACA vs Bernard et al: Interventions and Conclusion

	HACA 2002	Bernard et al 2002
Temperature Targets	32-34ºC vs normothermia	33ºC vs normothermia
Duration intervention	24 hours, then passive rewarming	18 hours, then active rewarming over 6 hours
Outcomes	**Mild hypothermia may have better neurologic outcomes and decreased mortality**	

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Nielsen et al (2013): Design

Objective
- Determine difference in mortality at 180 days in post-arrest patients when targeting 33ºC vs 36ºC

Methods
- Multicenter, randomized controlled trial

Population
- N = 939, shockable and nonshockable rhythm

Intervention
- 33ºC vs 36ºC, gradual rewarming at 28 hours by 0.5ºC/hour to target 37ºC

Nielsen N, Wetterslev J, Cronberg T, Erlinge D, Gasche Y, Hassager C, Horn J, Hovdenes J, Kjaergaard J, Kuiper M, Pellis T. Targeted temperature management at 33 C versus 36 C after cardiac arrest. New England journal of medicine. 2013 Dec 5;369(23):2197-206.

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Nielsen et al (2013): Conclusions

Conclusions
- No difference in mortality
- No difference in neurologic outcomes

Limitations
- High bystander CPR; unclear if contributory towards outcomes
- Less selective, thus hard to determine ideal population

Takeaways
- Targeting 33ºC vs 36ºC post-cardiac arrest was not associated with reduced all cause mortality or better neurologic outcomes

Nielsen N, Wetterslev J, Cronberg T, Erlinge D, Gasche Y, Hassager C, Horn J, Hovdenes J, Kjaergaard J, Kuiper M, Pellis T. Targeted temperature management at 33 C versus 36 C after cardiac arrest. New England journal of medicine. 2013 Dec 5;369(23):2197-206.

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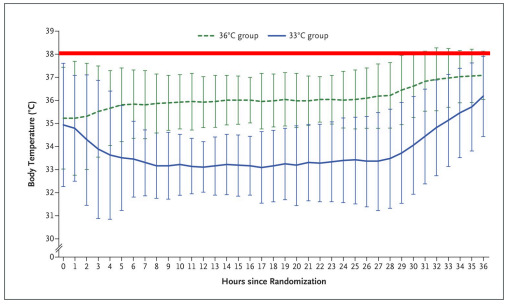
Nielson et al (2013) Fever Curve



Minimal to no hyperthermia

Nielsen N, Wetterslev J, Cronberg T, Erlinge D, Gasche Y, Hassager C, Horn J, Hovdenes J, Kjaergaard J, Kuiper M, Pellis T. Targeted temperature management at 33 C versus 36 C after cardiac arrest. New England journal of medicine. 2013 Dec 5;369(23):2197-206.

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HYPERION (2019): Design

Objectives

- Compare 33ºC vs 37ºC on neurologic outcomes at day 90 in patients with out-of-hospital cardiac arrests **with non-shockable rhythms**

Methods

- Open-label, multicenter, randomized controlled trial

Population

- N = 584, ~67 years old, 91-96% witnessed arrest, ~70% bystander CPR with non-shockable rhythm

Interventions

- Hypothermia: 33ºC for 24 hours with slow rewarming 0.25-0.5ºC/hour
- Normothermia: 36.5-37.5ºC for 48 hours

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HYPERION (2019): Conclusions

Conclusion

- Better neurologic outcomes in patients cooled to 33ºC vs 37ºC (10.2% vs 5.7%)

Limitations

- Telephone conversations to assess neurologic outcomes
- 10% of patients had unknown rhythms
- Control group was maintained at 37ºC

Takeaway

- Targeting 33ºC over 37ºC in patients with non-shockable rhythms leads to better neurologic outcomes

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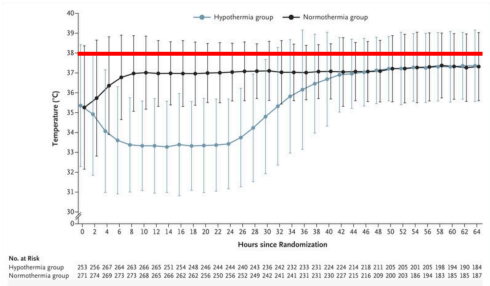
HYPERION Fever Curve



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Based on the 4 major trials, which of the following temperatures targets should be selected to have the highest likelihood of neurologic benefit?

A. 30ºC
B. 33ºC
C. 36ºC
D. 37ºC
E. The ideal target is still unclear

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Recommendations for Future Direction

- Evaluate:
  - Fever prevention vs strict temperature targets
  - Duration of cooling
  - Cooling in non-shockable rhythm
  - Medications for shivering management

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Conclusion

- Targeted temperature management in post-cardiac arrest patients may improve neurologic outcomes
- Avoid hyperthermia
- Temperature targets have varied
  - 36ºC vs 33-34ºC has not shown to have a difference in neurologic outcomes
- Pharmacists can help monitor for fever and educate others on anti-shivering therapies

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Thank You!

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Acknowledgement

- Thank you Cole Sloan, PharmD, BCPS, BCGP

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Questions?

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Supplemental Slide: Columbia Anti-Shivering Protocol

Step		Intervention	Dose
0	Baseline	Acetaminophen	650–1000 mg Q 4–6 h
		Buspirone	30 mg Q 8 h
		Magnesium sulfate	0.5–1 mg/h IV Goal (3–4 mg/dl)
		Skin counterwarming	43°C/MAX Temp
1	Mild sedation	Dexmedetomidine	0.2–1.5 mcg/kg/h
		or	Fentanyl starting dose 25 mcg/h
		Opioid	Meperidine 50–100 mg IM or IV
2	Moderate sedation	Dexmedetomidine and Opioid	Doses as above
3	Deep sedation	Propofol	50–75 mcg/kg/min
4	Neuromuscular blockade	Vecuronium	0.1 mg/kg IV

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