Penn State College of Medicine
Continuing Education

Seventh Annual Neurocritical Care Conference

Thursday, Oct. 23, 2025

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Targeted Temperature Management Medications in Neurocritical Care

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Objectives

Review literature supporting the efficacy of medications that are commonly utilized for targeted temperature management

Develop a patient specific targeted temperature management treatment plan

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Targeted temperature management (TTM) encompasses the following:

- Therapeutic hypothermia (TH)
  - Target temperature of 32-36 °C
- Controlled normothermia
  - Target temperature of 36-37.5 °C
- Treatment of fever
  - Target temperature of ≤ 37.5 °C

Madden LK, et al. *Neurocrit Care. 2017.*

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Targeted Temperature Management Recommendations

Neurocritical Care Society Guideline (2017):

- Provides a guideline for recommendations in patients who
- Lack of evidence regarding
  - Ideal site for TTM monitoring
  - Ideal duration of TTM
  - Use of pharmacological agents during cooling

European Society of Intensive Care Medicine (ESICM) and Neuro Anesthesia and Critical Care Society (NACCS) (2024):

- Temperature should be monitored continuously and fever promptly identified
- Controlled normothermia (36.0-37.5 °C) is strongly recommended in patients with traumatic brain injuries

Lavinio A, et al. Critical care. 2024.
Madden LK, et al. *Neurocrit Care. 2017.*

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Phases of TTM

Induction

Achieved via non-invasive or invasive methods

Goal temperature 32-36 °C

Maintenance

Target temperature achieved and maintained for approximately 24 hours

Rewarming

Starts approximately 24 hours after cooling via active or passive methods

Goal temperature 36-37.5 °C

Madden LK, et al. *Neurocrit Care. 2017.*

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Methods to Achieve TTM

Non-invasive
- Ice packs
- Surface cooling devices
- Cool intravenous fluid infusions

Invasive
- Endovascular catheters

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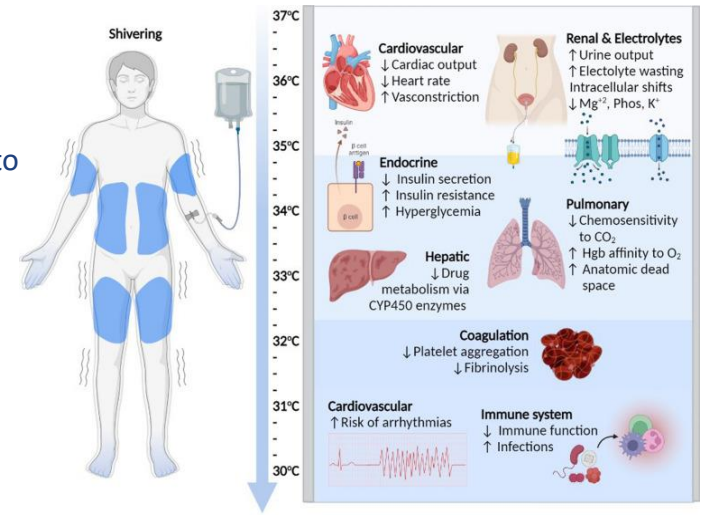
Shivering

- Thermoregulatory response to changes in temperature, leading to alterations in:
  - Metabolism
  - Oxygen consumption
  - Energy expenditure
  - Carbon dioxide production
- Metabolic consequences may outweigh clinical benefit of temperature control



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Medications Used in TTM

- Acetaminophen
- Buspirone
- Magnesium
- Analgesics and sedatives
  - Meperidine, Fentanyl
  - Dexmedetomidine, Clonidine
  - Propofol
- Neuromuscular blocking agents
  - Vecuronium

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Columbia Anti-Shivering Protocol

Table 1 The 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

TABLE 1. Bedside Shiver Assessment Scale

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

Choi HA, et al. *Neurocrit Care.* 2011.

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First Line Agents

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Acetaminophen

Role in therapy: First line agent for fever prevention and maintenance of normothermia

Mechanism	Dose	Pharmacokinetics	Adverse Effects
Antipyresis via inhibition of the hypothalamic heat-regulating center	PO/IV: 650-1000 mg q4-8h Max: 4000 mg per day	Onset: 30-60 min Duration: 4-6 hours Half-life, elimination: 2-3 hours	Hepatotoxicity Nausea Vomiting

Lexicomp. Acetaminophen. 2025.

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Buspirone

Role in therapy: First line agent for anti-shivering

Mechanism	Dose	Pharmacokinetics	Adverse Effects
High affinity partial agonist for 5-HT1a receptors, weak affinity for 5-5HT2 receptors, moderate affinity for dopamine D2 receptors	PO: 30 mg q8h	Time to peak: 40-90 min Half-life, elimination: 2-3 hours AUC increased in renal impairment	Dizziness Headache Drowsiness Dyskinesia, akathisia Nausea Serotonin syndrome

Lexicomp. Buspirone. 2025.

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Buspirone Literature

Retrospective observational cohort study at a large academic medical center including out-of-hospital cardiac arrest (OHCA) or in-hospital cardiac arrest (IHCA) patients who underwent TTM targeted to 33 °C

Intervention Groups:

- Pre-protocol group (N=51)
- Post-protocol group (N=80)

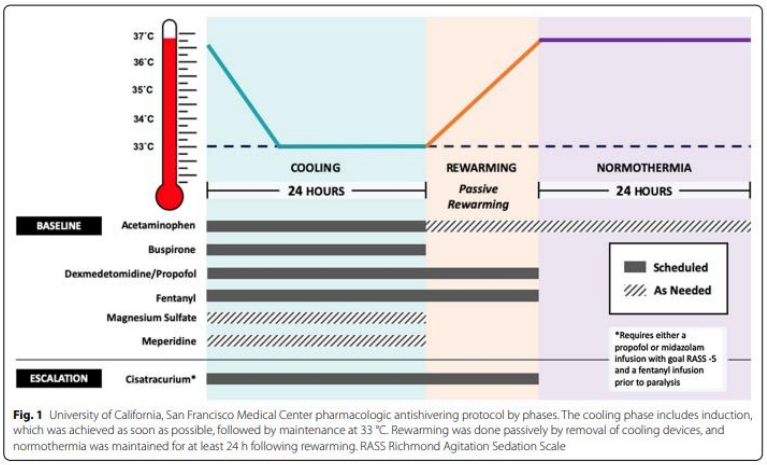

Fig. 1 University of California, San Francisco Medical Center pharmacologic antishivering protocol by phases. The cooling phase includes induction, which was achieved as soon as possible, followed by maintenance at 33 °C. Rewarming was done passively by removal of cooling devices, and normothermia was maintained for at least 24 h following rewarming. RASS Richmond Agitation Sedation Scale

Huynh C, et al. *Neurocrit Care.* 2022.

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Table 1 UCSF Medical Center pharmacologic antishivering protocol

	Intervention	Dose
Baseline	Scheduled	
	Acetaminophen	1000 mg per FT or IV Q6H[a]
	Buspirone	30 mg per FT Q8H
	Dexmedetomidine	0–1.2 µg/kg/h, targeting RASS[b] score of − 3 (range − 4 to − 2)
	Propofol	0–75 µg/kg/min, targeting RASS[b] score of − 3 (range − 4 to − 2)
	Fentanyl	25 µg IV Q15min PRN for pain and 0–100 µg/h titrated to CPOT[c] < 3
	As needed	
	Magnesium sulfate	2 g IV Q6H PRN for serum magnesium < 2.5 mg/dL
	Meperidine	12.5–25 mg IV Q4H PRN for BSAS > 0 × 24 h (not to exceed 75 mg/24 h)
Escalation	Cisatracurium	0.15–0.2 mg/kg IV once followed by 0–5 µg/kg/min titrated to BSAS score of 0 (requires either a propofol or midazolam infusion with goal RASS score of − 5 and a fentanyl infusion prior to paralysis)

CPOT Critical Care Pain Observation Tool, *FT* feeding tube, *IV* intravenously, *PRN* as needed, Q15min, every 15 min, Q4H, every 4 h, Q6H, every 6 h, Q8H, every 8 h, *RASS* Richmond Agitation Sedation Scale

[a] 500 mg per FT or IV Q6H for patients with hepatic insufficiency

[b] RASS scores: − 5, unarousable sedation; − 4, deep sedation; − 3, moderate sedation; − 2, light sedation; − 1, drowsy; 0, alert and calm; 1, restless; 2, agitated; 3, very agitated; 4, combative

[c] CPOT ≤ 2, minimal to no pain present; CPOT > 2, unacceptable level of pain

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Results

Primary outcome:
- Incidence of shivering between groups

Secondary outcomes:
- Time from arrest to goal body temperature
- Total time spent at goal body temperature
- Percentage alive at discharge

Results:
- Incidence of patients with shivering was significantly reduced in the post-protocol group (57% vs. 39%, *p*=0.03)

Medication	Pre-protocol (n=51)	Post-protocol (n=80)	P value
Acetaminophen	6 (12)	52 (55)	<0.01
Buspirone	2 (4)	58 (73)	<0.01
Meperidine	4 (8)	26 (34)	<0.01
Dexmedetomidine	2 (4)	15 (19)	0.02
Fentanyl	43 (84)	64 (80)	0.65
Midazolam	7 (14)	6 (8)	0.4
Propofol	49 (96)	63 (79)%	0.01

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Magnesium

Role in therapy: First line adjunct agent for anti-shivering

Mechanism	Dose	Pharmacokinetics	Adverse Effects
Reduces smooth muscle tone and vasodilation, leading to reduced shivering	IV: 1-2 grams Target serum level of 3-4 mg/dL	Onset: Immediate	Flushing Hypotension Vasodilation Caution in myasthenia gravis

Lexicomp. Magnesium. 2025.

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Analgesics, Sedatives and Paralytics

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Dexmedetomidine and Clonidine

Role in therapy: Non-intubated patients with shivering refractory to first line agents

Drug	Mechanism	Dose	Pharmacokinetics	Adverse Effects
Clonidine	Alpha 2-adrenoreceptor agonism within the brain stem leading to anesthetic and sedative effects	PO: 0.1-0.3 mg q6-8 hours	Onset: 30-60 min Peak: 2-4 hours T ½ : 12-16 hours, prolonged in renal impairment	Hypotension Bradycardia Rebound hypertension Withdrawal
Dexmedetomidine		IV, continuous infusion: 0.2-1.5 mcg/kg/hour	Onset: 5-10 min Peak: 60 min Duration: 1-4 hours, prolonged in hepatic impairment	Hypotension Bradycardia Tachyphylaxis Withdrawal

Lexicomp. Clonidine. 2025.
Lexicomp. Dexmedetomidine. 2025.

Dexmedetomidine and Buspirone

Single center study of 8 healthy male volunteers to assess the effects of the combination of buspirone and dexmedetomidine on the shiver threshold

Interventions:

- Active cooling using Lactated Ringers to decrease tympanic membrane temperature by 1.5°C/h
  - Buspirone 60 mg PO
  - Dexmedetomidine IV infusion to target serum level 0.6 ng/ml
  - Combination of buspirone 60 mg PO and dexmedetomidine

Results:

- Buspirone reduced the shivering threshold from 36.6°C +/- 0.4°C to 35.9°C +/- 0.4°C, dexmedetomidine reduced it to 34.7°C +/- 0.5°C, and the combination to 34.1 +/- 0.4°C

Lenhardt R, et al. *Anesthesiology.* 2009.

Opioids

Drug	Mechanism	Dose	Pharmacokinetics	Adverse Effects
Meperidine	Binds to opioid receptors in the CNS, causing inhibition of ascending pain pathways and generalized CNS depression	IV: 12.5-50 mg once for post-operative shivering	Onset: 5 minutes Peak effect: 5-7 minutes Duration: 2-3 hours Half-life, elimination: 2.5-4 hours, 7-11 hours in liver disease	Bradycardia Hypotension Flushing
Fentanyl		IV, intermittent: 25-50 mcg q30-60 min or prn IV, continuous infusion: 25-250 mcg/hour	Onset: immediate Duration: 30-60 minutes Half-life elimination: 5 hours, prolonged with continuous infusion	Respiratory depression Constipation Hypotension Bradycardia Confusion

Lexicomp. Meperidine. 2025.
Lexicomp. Fentanyl. 2025

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Buspirone and Meperidine

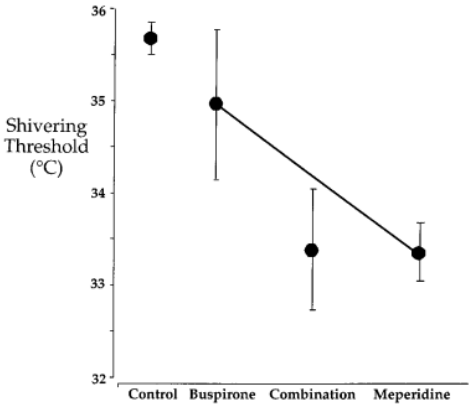
Single center study including eight healthy male volunteers to assess meperidine and buspirone alone and in combination on reduction of the shivering threshold

Interventions:

- Active cooling using Lactated Ringers and circulating water to mean skin temperature of 32 ˚C
  - Meperidine target plasma concentration 0.8 ug/mL
  - Meperidine (0.4 ug/mL) plus buspirone 30 mg
  - Buspirone 60 mg

Results:

- Combination of meperidine and buspirone synergistically lowered the shivering threshold to 33.4 °C +/- 0.7 °C while being less sedating than high dose meperidine alone



Mokhtarani M, et al. *Anesth Analg.* 2001.

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Propofol

Role in therapy: Second line agent for intubated patients refractory to other agents who require deep sedation

Mechanism	Dose	Pharmacokinetics	Adverse Effects
GABA-a receptor agonist resulting in a reduction of glutamatergic activity through NMDA receptor blockage	IV continuous infusion: 5-75 mcg/kg/min	Onset: rapid, 3-5 min Duration: 10-15 min T ½: biphasic, 40 min then 4-7 hours	Hypotension Bradycardia Hypertriglyceridemia Propofol related infusion syndrome

Lexicomp. Propofol. 2025.

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Neuromuscular Blocking Agents for Shivering

- Role in therapy: For intubated patients refractory to first line agents and sedatives for shiver control

Drug	Mechanism	Dose	Pharmacokinetics	Adverse Effects
Cisatracurium	Blocks acetylcholine from binding to receptors on motor endplate inhibiting depolarization, inhibition of neural transmission	IV, continuous infusion: 0.1-0.2 mg/kg loading dose followed by 1-3 mcg/kg/min	Onset: 1-3 minutes Duration: 35-45 minutes Half-life, elimination: 22-29 minutes	Bronchospasm Hypotension Bradycardia
Vecuronium		IV, intermittent: 0.1-0.2 mg/kg up to 8-12 mg IV, continuous infusion: 0.08-0.1 mg/kg loading dose, followed by 0.8-1.2 mcg/kg/min	Onset: within 2-4 minutes Duration: 25-40 minutes Half-life, elimination: 65-75 minutes Caution in hepatic impairment	Bradycardia Flushing Hypersensitivity reactions

Lexicomp. Cisatracurium. 2025.
Lexicomp. Vecuronium. 2025.

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Medication	Role in Therapy	Dose	Clinical Pearls
Acetaminophen	First line for fever prevention	PO/IV: 650-1000 mg q4-8h Max: 4000 mg per day	Multiple routes available Should be scheduled Caution in hepatic impairment
Buspirone	First line for shiver prevention	PO: 30 mg q8h	Only available orally
Magnesium	First line adjunct agent	IV: 1-2 grams	Target serum levels may vary by protocol
Meperidine	Adjunct, typically for post-operative shivering	IV: 12.5-50 mg once for post-operative shivering	Often used post-surgically Critical shortage
Fentanyl	Adjunct for analgesia and sedation	IV, intermittent: 25-50 mcg q30-60 min IV, continuous infusion: 25-250 mcg/hour	Available IV push or continuous infusion for intubated patients
Dexmedetomidine	Non-intubated or intubated patients requiring agitation control or light-moderate sedation	IV, continuous infusion: 0.2-1.5 mcg/kg/hour	Provides light sedation Bradycardia, hypotension
Clonidine		PO: 0.1-0.3 mg q6-8 hours	Can use to taper dexmedetomidine in agitated patients
Propofol	Intubated patients requiring deep sedation	IV continuous infusion: 5-75 mcg/kg/min	Hypertriglyceridemia Hypotension, bradycardia
Cisatracurium	For intubated patients requiring deep sedation and paralysis	IV, continuous infusion: 0.1-0.2 mg/kg loading dose followed by 1-3 mcg/kg/min	Hypothermia may prolong duration of action Last line for intubated patients only Continuous use should be reassessed frequently
Vecuronium		IV, intermittent: 0.1-0.2 mg/kg up to 8-12 mg IV, continuous infusion: 0.08-0.1 mg/kg loading dose, followed by 0.8-1.2 mcg/kg/min	

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References

1. Madden LK, Hill M, May TL, et al. The Implementation of Targeted Temperature Management: An Evidence-Based Guideline from the Neurocritical Care Society. *Neurocrit Care*. 2017;27(3):468-487. doi:10.1007/s12028-017-0469-5
2. Lavinio, Andrea et al. "Targeted temperature control following traumatic brain injury: ESICM/NACCS best practice consensus recommendations." *Critical care (London, England)* vol. 28,1 170. 20 May. 2024, doi:10.1186/s13054-024-04951-x
3. Choi HA, Ko SB, Presciutti M, et al. Prevention of shivering during therapeutic temperature modulation: the Columbia anti-shivering protocol. *Neurocrit Care*. 2011;14(3):389-394. doi:10.1007/s12028-010-9474-7
4. Lexicomp. (2025). Acetaminophen. In Lexi-Drugs Online. Retrieved [10/1/2025]
5. Lexicomp. (2025). Buspirone. In Lexi-Drugs Online. Retrieved [10/1/2025]
6. Huynh C, Lui J, Behbahani V, Thompson Quan A, Morris A, Baumgartner L. Pre Versus Post Implementation of a Pharmacologic Antishivering Protocol During Targeted Temperature Management Following Cardiac Arrest. *Neurocrit Care*. 2022;36(2):511-518. doi:10.1007/s12028-021-01327-9
7. Lexicomp. (2025). Magnesium. In Lexi-Drugs Online. Retrieved [10/1/2025]
8. Lexicomp. (2025). Clonidine. In Lexi-Drugs Online. Retrieved [10/1/2025]
9. Lexicomp. (2025). Dexmedetomidine. In Lexi-Drugs Online. Retrieved [10/1/2025]
10. Lenhardt R, Orhan-Sungur M, Komatsu R, et al. Suppression of shivering during hypothermia using a novel drug combination in healthy volunteers. *Anesthesiology*. 2009;111(1):110-115. doi:10.1097/ALN.0b013e3181a979a3
11. Lexicomp. (2025). Meperidine. In Lexi-Drugs Online. Retrieved [10/1/2025]
12. Lexicomp. (2025). Fentanyl. In Lexi-Drugs Online. Retrieved [10/1/2025]
13. Lexicomp. (2025). Cisatracurium. In Lexi-Drugs Online. Retrieved [10/1/2025]
14. Lexicomp. (2025). Vecuronium. In Lexi-Drugs Online. Retrieved [10/1/2025]

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