Therapeutic Hypothermia in Traumatic Brain Injury

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Learning Objectives

- Review cellular processes motivating therapeutic hypothermia in traumatic brain injury
- Explore successes with therapeutic hypothermia in animal models and their potential translation into successes in humans
- Appreciate the application of therapeutic hypothermia in the human traumatic brain injury population

Sydney J

- 79YO female found down at home by her daughter with last known well 10 hours earlier when she left for work
- Daughter noticed large hematoma at right zygomatic region

- Atrial fibrillation on rivaroxaban
- Dementia on memantine, donepezil
- Dyslipidemia on atorvastatin
- Epilepsy on phenytoin
- GERD on omeprazole
- HTN on carvedilol
- Epilepsy on phenytoin
- Right MCA stroke

- Daughter called 911
- EMS found patient with minimal speech and left hemiparesis (NOT baseline)
- Subsequently manifested agonal respirations and hypotension
- Daughter confirmed FULL CODE status
- EMS inserted LMA
- EMS started IVF for hypotension
- Transported to nearest neurotrauma center with Stroke Alert call
- Stroke Team met patient at trauma bay

Sydney J

97F

128/min

84/32mmHg

90% on 80% FiO2 (LMA)

Unresponsive, GCS 3T

Large hematoma at right zygoma

Pupils minimally reactive, corneal reflex absent

Cough reflex absent, gag reflex absent

LMA in place

Irregular rate, irregular rhythm, no murmur

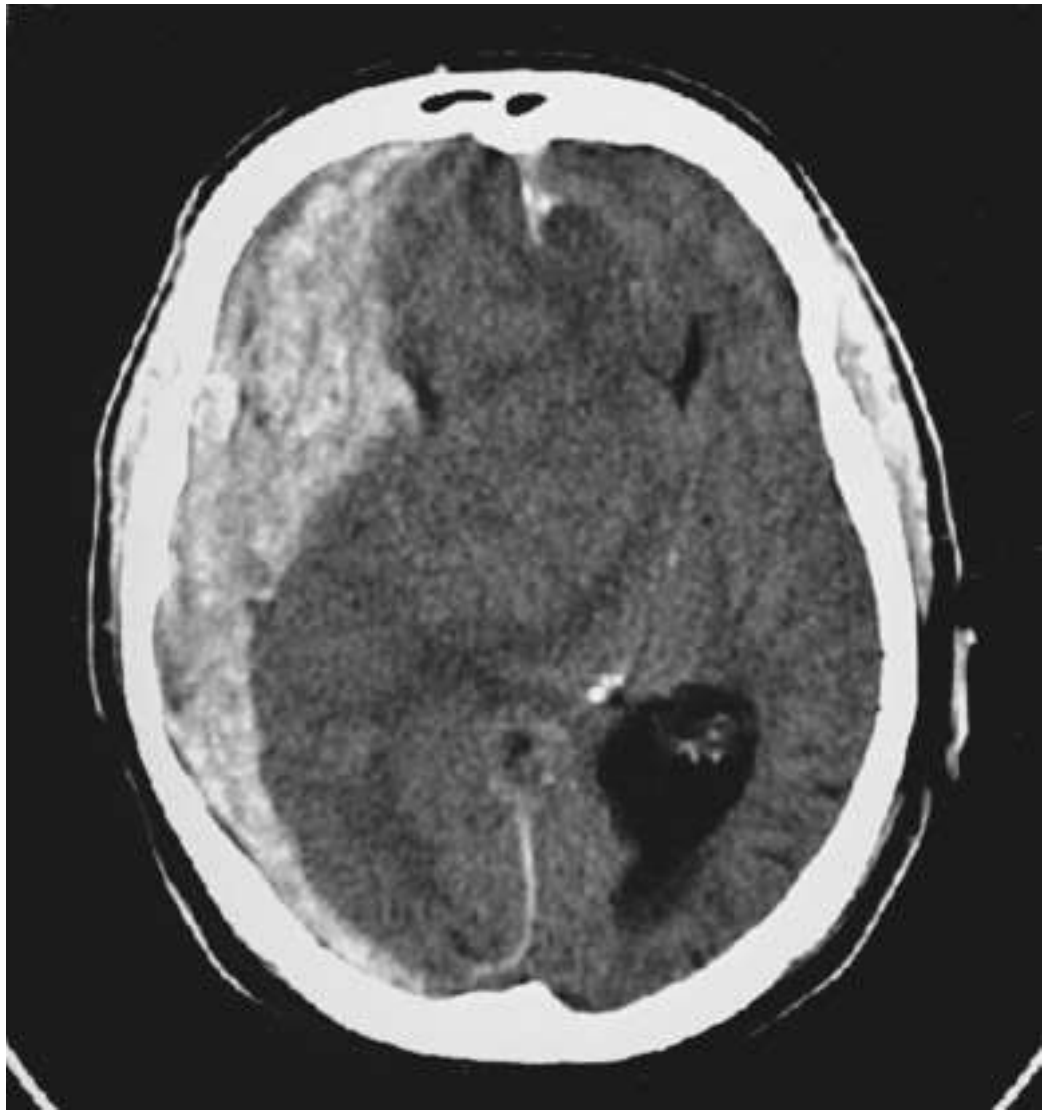
No wheezes, no crackles, does not overbreathe mechanical ventilator

Soft abdomen, non-distended abdomen

No Foley catheter

Decerebrate posturing at UE B/L

Decerebrate posturing at LE B/L



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Initial Considerations

- It’s not good!
- Look at the Neurologist…
- Definitely not a tPA candidate
- Get a Neurosurgery consult STAT
- Insert an endotracheal tube
- Initiate another fluid bolus +/- vasopressor agent
- Talk to daughter about goals of care

- Mannitol?
- Hypertonic saline?
- PCC (K-CENTRA)?
- Andexanet alpha (ANDEXXA)?
- Therapeutic hypothermia?

- Decompressive hemicraniectomy?
- Hospice?
- Referral to OPO?

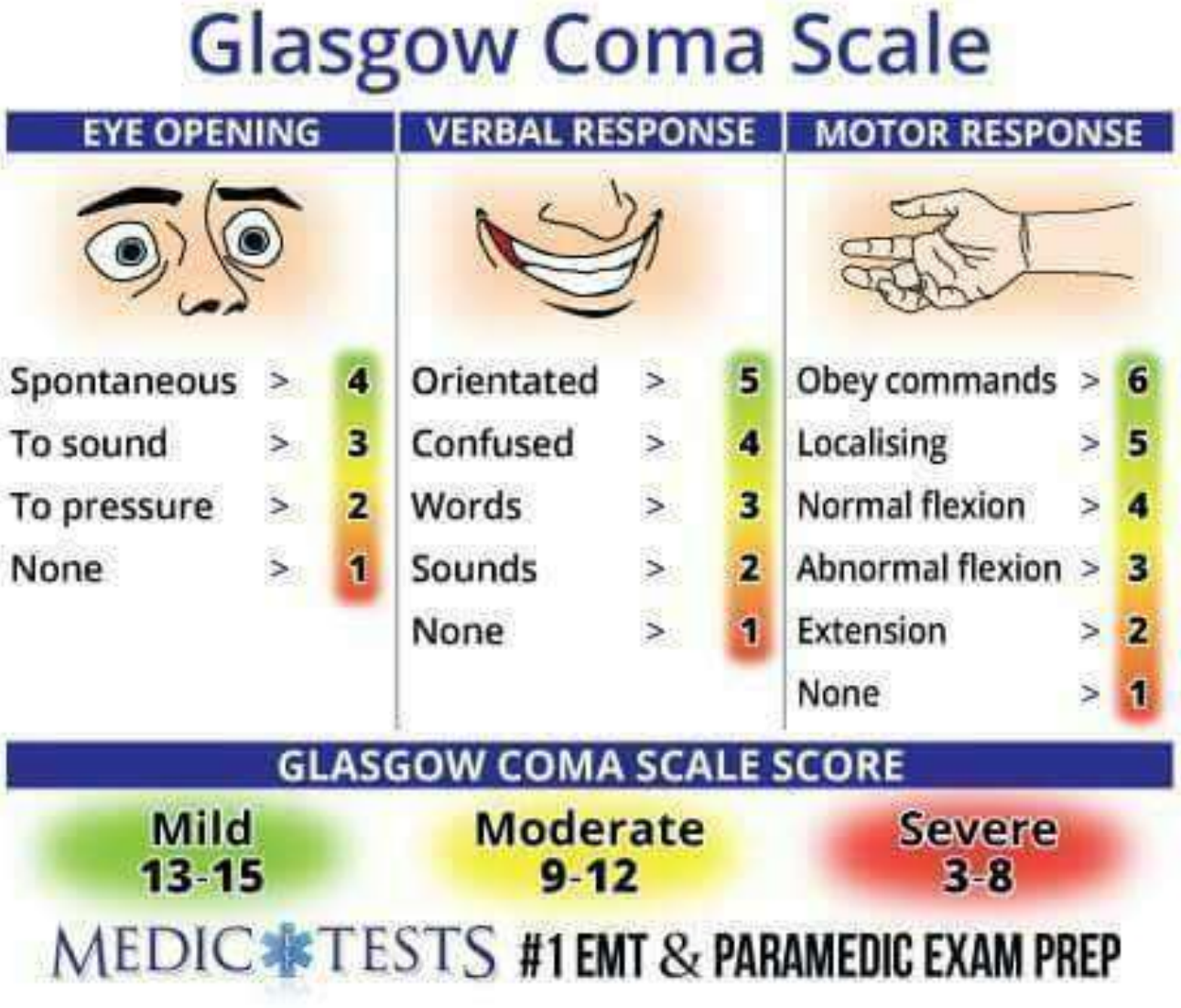
Burden of Pathology

- $76.5B economic impact (2010)
- 2.5M emergency department encounters (2013)
- 223,000 hospitalizations (2019)
- 64,000 mortalities (2020)

- Highest risk group: >75YO
- Higher risk sex: Male
- Rural mortality
- Access to care disparity

https://www.cdc.gov/traumaticbraininjury/images/severe_TBI_five-year_outcomes.PNG
https://www.cdc.gov/traumaticbraininjury/data/index.html

Traumatic Brain Injury



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Motivations for Therapeutic Hypothermia

- TBI Phase 1: Direct Tissue Damage
  - Aerobic to anaerobic shift in metabolism
  - Increased membrane permeability
  - CEREBRAL EDEMA

- TBI Phase 2: Opening of Ion Channels
  - Inadequate ATP availability
  - Increased glutamate and aspartate release
  - Intracellular calcium shift
  - Activation of enzymes resulting in apoptosis
  - CEREBRAL EDEMA

Motivations for Therapeutic Hypothermia

- Monro-Kellie doctrine

- Reduced cerebral blood flow
- Decreased cerebral oxygen consumption
- Decreased carbon dioxide production
- Oxyhemoglobin dissociation curve to the left
- Increased integrity of blood brain barrier
- Decreased inflammatory cascade
- Decreased caspase 3 and cytochrome C (apoptosis)

- Limiting secondary brain injury

Motivations for Therapeutic Hypothermia

Table 1 Type and pathophysiology of traumatic brain injury

	Diffuse brain injury	Focal brain injury
Primary brain injury	• Diffuse axonal injury • Petechial white matter hemorrhage with diffuse vascular injury	• Focal cortical contusion • Intracerebral hemorrhage • Extracerebral hemorrhage (i.e., ASDH, AEDH)
Secondary brain injury	• Delayed neuronal injury • Diffuse brain swelling • Diffuse ischemic injury • Diffuse hypoxic injury • Diffuse metabolic dysfunction	• Delayed neuronal injury • Focal brain swelling • Focal ischemic injury • Focal hypoxic injury • Regional metabolic dysfunction

ASDH acute subdural hematoma, *AEDH* acute epidural hematoma

Yokobori, S. and H. Yokota. "Targeted temperature management in traumatic brain injury." *Journal of Intensive Care*. 4(28). 2016.

Motivations for Therapeutic Hypothermia

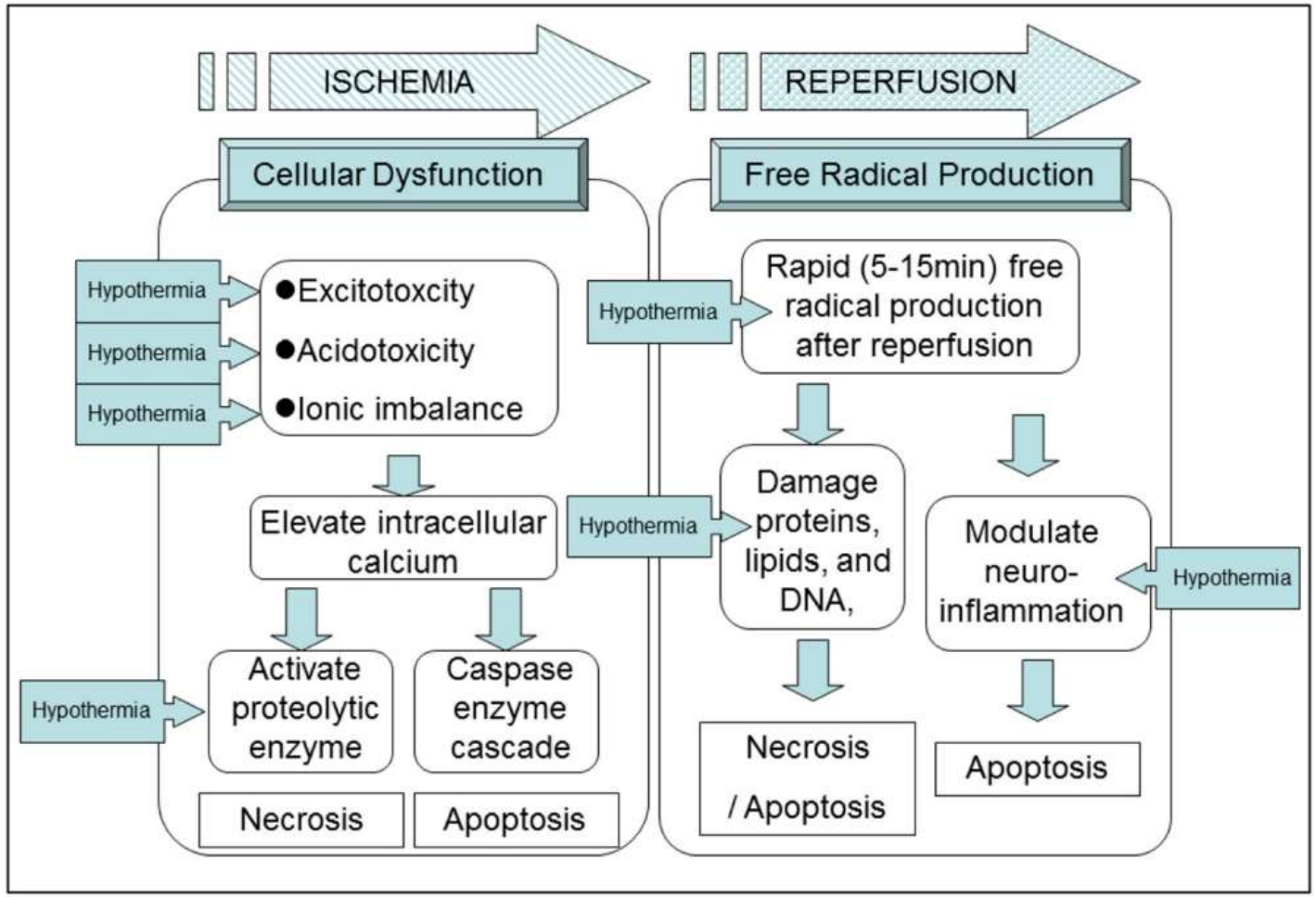


Fig. 1 The schema of mechanisms of ischemic/reperfusional (I/R) brain injury and the effective point of hypothermia treatment. The pathology of I/R injury is approximately separated as two mechanisms, i.e., the cell death following cellular dysfunction in ischemic phase and the free radical production in reperfusion phase. The *boxed arrow* with entered "Hypothermia" means the estimated effective points in I/R cascade

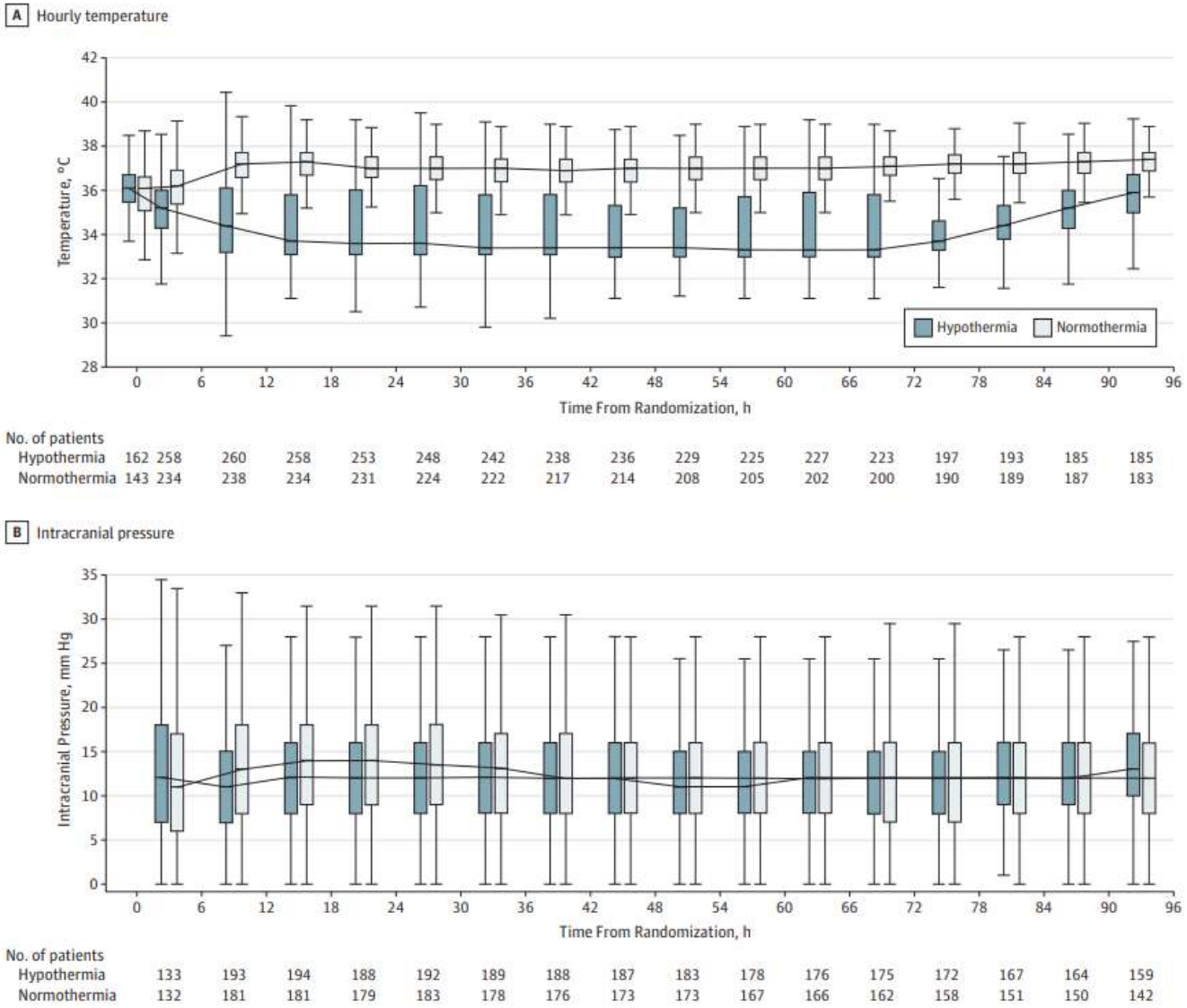
Yokobori, S. and H. Yokota. "Targeted temperature management in traumatic brain injury." *Journal of Intensive Care*. 4(28). 2016.

Animal Model Success Stories

- Lateral fluid percussion injury in rats (motor recovery)
- Reduced brain contusion volume
- Reduced blood brain barrier damage
- Reduced diffuse axonal injury
- Improved oligodendrocyte survival

Application of Therapeutic Hypothermia to Human Adults

Figure 2. Hourly Temperature and Intracranial Pressure for the First 4 Days (96 hours) Postrandomization (N = 500)



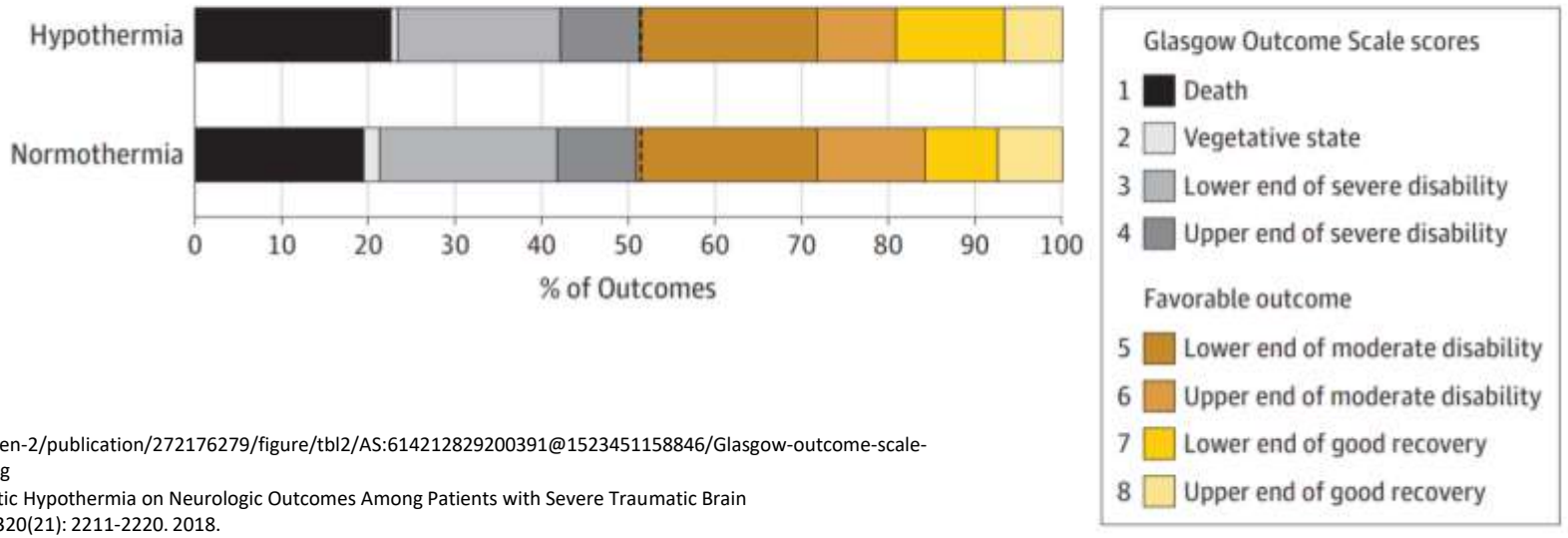
Cooper, D., et al. "Effect of Early Sustained Prophylactic Hypothermia on Neurologic Outcomes Among Patients with Severe Traumatic Brain Injury: The POLAR Randomized Clinical Trial." *JAMA*. 320(21): 2211-2220. 2018.

Application of Therapeutic Hypothermia to Human Adults

GOS	GOSE	Interpretation
1 = Dead	1 = Dead	Dead
2 = Vegetative state	2 = Vegetative state	Absence of awareness of self and environment
3 = Severe disability	3 = Lower severe disability	Needs full assistance in ADL
	4 = Upper severe disability	Needs partial assistance in ADL
4 = Moderate disability	5 = Lower moderate disability	Independent, but cannot resume work/school or all previous social activities
	6 = Upper moderate disability	Some disability exists, but can partly resume work or previous activities
5 = Good recovery	7 = Lower good recovery	Minor physical or mental deficits that affects daily life
	8 = Upper good recovery	Full recovery or minor symptoms that do not affect daily life

ADL = activities of daily living.

Figure 3. Distribution of Glasgow Outcome Scale–Extended Scores at 6 Months After Randomization



https://www.researchgate.net/profile/Alexander-Olsen-2/publication/272176279/figure/tbl2/AS:614212829200391@1523451158846/Glasgow-outcome-scale-GOS-and-Glasgow-outcome-scale-extended-GOSE.png

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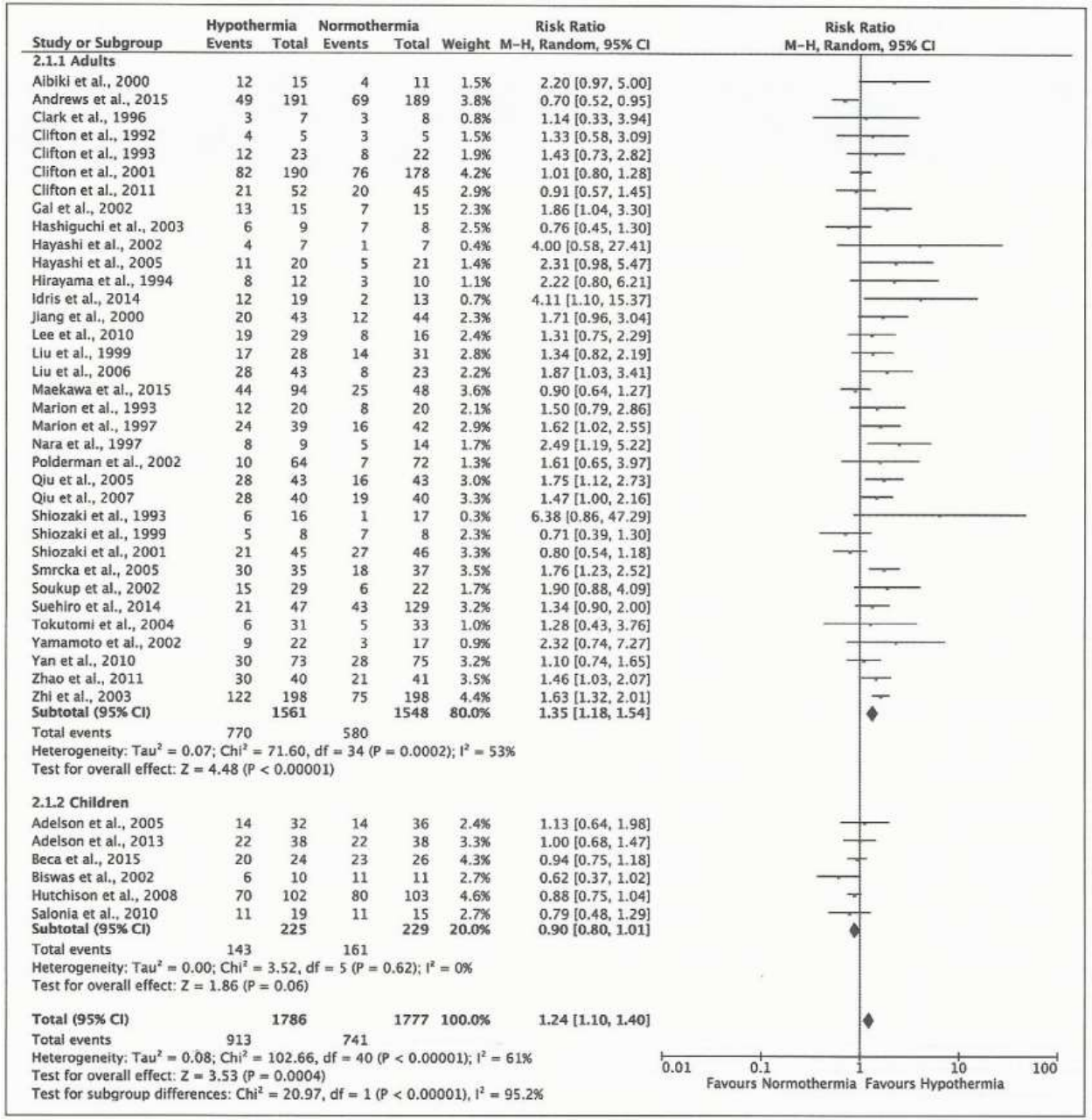
Application of Therapeutic Hypothermia to Human Adults



Study or Subgroup	Hypothermia Events	Hypothermia Total	Normothermia Events	Normothermia Total	Weight	Risk Ratio M-H, Random, 95% CI
2.1.1 Adults						
Aibiki et al., 2000	12	15	4	11	1.5%	2.20 [0.97, 5.00]
Andrews et al., 2015	49	191	69	189	3.8%	0.70 [0.52, 0.95]
Clark et al., 1996	3	7	3	8	0.8%	1.14 [0.33, 3.94]
Clifton et al., 1992	4	5	3	5	1.5%	1.33 [0.58, 3.09]
Clifton et al., 1993	12	23	8	22	1.9%	1.43 [0.73, 2.82]
Clifton et al., 2001	82	190	76	178	4.2%	1.01 [0.80, 1.28]
Clifton et al., 2011	21	52	20	45	2.9%	0.91 [0.57, 1.45]
Gal et al., 2002	13	15	7	15	2.3%	1.86 [1.04, 3.30]
Hashiguchi et al., 2003	6	9	7	8	2.5%	0.76 [0.45, 1.30]
Hayashi et al., 2002	4	7	1	7	0.4%	4.00 [0.58, 27.41]
Hayashi et al., 2005	11	20	5	21	1.4%	2.31 [0.98, 5.47]
Hirayama et al., 1994	8	12	3	10	1.1%	2.22 [0.80, 6.21]
Idris et al., 2014	12	19	2	13	0.7%	4.11 [1.10, 15.37]
Jiang et al., 2000	20	43	12	44	2.3%	1.71 [0.96, 3.04]
Lee et al., 2010	19	29	8	16	2.4%	1.31 [0.75, 2.29]
Liu et al., 1999	17	28	14	31	2.8%	1.34 [0.82, 2.19]
Liu et al., 2006	28	43	8	23	2.2%	1.87 [1.03, 3.41]
Maekawa et al., 2015	44	94	25	48	3.6%	0.90 [0.64, 1.27]
Marion et al., 1993	12	20	8	20	2.1%	1.50 [0.79, 2.86]
Marion et al., 1997	24	39	16	42	2.9%	1.62 [1.02, 2.55]
Nara et al., 1997	8	9	5	14	1.7%	2.49 [1.19, 5.22]
Polderman et al., 2002	10	64	7	72	1.3%	1.61 [0.65, 3.97]
Qiu et al., 2005	28	43	16	43	3.0%	1.75 [1.12, 2.73]
Qiu et al., 2007	28	40	19	40	3.3%	1.47 [1.00, 2.16]
Shiozaki et al., 1993	6	16	1	17	0.3%	6.38 [0.86, 47.29]
Shiozaki et al., 1999	5	8	7	8	2.3%	0.71 [0.39, 1.30]
Shiozaki et al., 2001	21	45	27	46	3.3%	0.80 [0.54, 1.18]
Smrcka et al., 2005	30	35	18	37	3.5%	1.76 [1.23, 2.52]
Soukup et al., 2002	15	29	6	22	1.7%	1.90 [0.88, 4.09]
Suehiro et al., 2014	21	47	43	129	3.2%	1.34 [0.90, 2.00]
Tokutomi et al., 2004	6	31	5	33	1.0%	1.28 [0.43, 3.76]
Yamamoto et al., 2002	9	22	3	17	0.9%	2.32 [0.74, 7.27]
Yan et al., 2010	30	73	28	75	3.2%	1.10 [0.74, 1.65]
Zhao et al., 2011	30	40	21	41	3.5%	1.46 [1.03, 2.07]
Zhi et al., 2003	122	198	75	198	4.4%	1.63 [1.32, 2.01]
Subtotal (95% CI)		**1561**		**1548**	**80.0%**	**1.35 [1.18, 1.54]**
Total events	770		580			
Heterogeneity: $Tau^2 = 0.07$; $Chi^2 = 71.60$, df = 34 (P = 0.0002); $I^2 = 53\%$						
Test for overall effect: Z = 4.48 (P < 0.00001)						
2.1.2 Children						
Adelson et al., 2005	14	32	14	36	2.4%	1.13 [0.64, 1.98]
Adelson et al., 2013	22	38	22	38	3.3%	1.00 [0.68, 1.47]
Beca et al., 2015	20	24	23	26	4.3%	0.94 [0.75, 1.18]
Biswas et al., 2002	6	10	11	11	2.7%	0.62 [0.37, 1.02]
Hutchison et al., 2008	70	102	80	103	4.6%	0.88 [0.75, 1.04]
Salonia et al., 2010	11	19	11	15	2.7%	0.79 [0.48, 1.29]
Subtotal (95% CI)		**225**		**229**	**20.0%**	**0.90 [0.80, 1.01]**
Total events	143		161			
Heterogeneity: $Tau^2 = 0.00$; $Chi^2 = 3.52$, df = 5 (P = 0.62); $I^2 = 0\%$						
Test for overall effect: Z = 1.86 (P = 0.06)						
Total (95% CI)		**1786**		**1777**	**100.0%**	**1.24 [1.10, 1.40]**
Total events	913		741			
Heterogeneity: $Tau^2 = 0.08$; $Chi^2 = 102.66$, df = 40 (P < 0.00001); $I^2 = 61\%$						
Test for overall effect: Z = 3.53 (P = 0.0004)						
Test for subgroup differences: $Chi^2 = 20.97$, df = 1 (P < 0.00001), $I^2 = 95.2\%$						

Crompton, E., et al. "Meta-Analysis of Therapeutic Hypothermia for Traumatic Brain Injury in Adult and Pediatric Patients." *Critical Care Medicine*. 45(4): 575-583. 2017.

Metabolic Changes with Therapeutic Hypothermia

- Hypokalemia
- Hyperkalemia
- Insulin resistance
- Coagulopathy

Complications Associated with Therapeutic Hypothermia

- Shivering
- Pneumonia
- Bradyarrhythmia
- Cold diuresis
- Decreased drug metabolism

Table Bedside Shivering Assessment Scale[a]

Score	Type of shivering	Location
0	None	No shivering is detected on palpation of the masseter, neck, or chest muscles
1	Mild	Shivering localized to the neck and thorax only
2	Moderate	Shivering involves gross movement of the upper extremities (in addition to neck and thorax)
3	Severe	Shivering involves gross movements of the trunk and upper and lower extremities

[a] Data from Badjatia et al.[16]

TABLE 2. Suggested Antishivering Protocol

When to Initiate	Typical BSAS Score at Initiation	Intervention	Dose	Goal of Intervention
Before starting temperature management, administer all 3 medications in this category.	0	Acetaminophen	650–1000 mg PO/PR/ NGT mg Q 4–6 h	Prevention of shivering
		Buspirone	30 mg PO/PR/NGT Q 8	
		Magnesium sulfate	0.5–1 g/h IV or 4g bolus; goal serum magnesium level of 3–4 mg/dL	
		Skin counterwarming	43°C/MAX Temp	
When shivering is localized to the neck/thorax; may be seen only as an artifact on ECG or felt by palpation	1	Dexmedetomidine or opioid	Dexmedetomidine 0.2–1.5 mcg/kg/h Fentanyl starting dose, 25 mcg/h Meperidine 50–100 mg IM or IV	Mild sedation
When shivering includes intermittent involvement of the upper extremities ± thorax	2	Dexmedetomidine and opioid	As above Consider continuous IV infusion of fentanyl 0.25–2 mcg/kg/h	Moderate sedation
When generalized shivering or sustained upper/lower-extremity shivering is present	3	Propofol	25–75 mcg/kg/min	Deep sedation
When generalized shivering or sustained upper/lower-extremity shivering is present despite use of medications at preceding levels	3	Rocuronium bolus or cisatracurium infusion or vecuronium bolus or pancuronium bolus	0.3–0.9 mg/kg 1–2 mcg/kg/min 0.08 – 0.1 mg/kg IV 0.04 – 0.1 mg/kg IV	Neuromuscular blockade, last resort after inability to control shivering despite all other medications

Note. If shivering worsens, add sequential interventions as appropriate after increasing numerical score of the BSAS, but continue all lower level interventions. Additional medications in the above classes may also be considered, such as ondansetron, tramadol, ketamine, etc.

https://pbrainmd.wordpress.com/2015/12/07/the-columbia-anti-shivering-protocol/

Jain, A., et al. "Shivering Treatments for Targeted Temperature Management: A Review." *Journal of Neuroscience Nursing*. 50(2): 63-67. 2018.

Clinical Considerations

- Target for therapeutic hypothermia
- Duration of therapeutic hypothermia
  - Peak cerebral edema
- Means for achieving therapeutic hypothermia
  - External cooling
  - Internal cooling catheter

Therapeutic Hypothermia
v.
Controlled Normothermia

Sydney J

- Neurosurgery deemed patient a poor candidate for surgery
- No PCC, andexanet-alpha, mannitol, hypertonic saline
- Single vasopressor agent maintained to achieve MAP>65mmHg
- Neurologic examination worsened, suggestive of brain death
- Apnea test completed (consistent with brain death)
- Two physicians documented brain death examinations
- Patient declared brain dead
- Daughter elected against organ procurement

Concluding Thoughts

- Therapeutic hypothermia in traumatic brain injury is NOT considered standard of care
- Therapeutic hypothermia in traumatic brain injury theoretically makes clinical sense and works in animal models
- Therapeutic hypothermia in traumatic brain injury is NOT considered standard of care
- Future research in therapeutic hypothermia and targeted temperature management may affect applicability of these therapies to human models
- Therapeutic hypothermia in traumatic brain injury is NOT considered standard of care

Question 1

Which of the following outcomes is supported by therapeutic hypothermia at traumatic brain injury?

A. Increased intracranial pressure/ICP
B. Increased free radical formation
C. Increased metabolic rate
D. Decreased permeability of the blood brain barrier
E. Decreased calcium efflux from cells

Question 2

Which of the following options is a feared and frequent complication of therapeutic hypothermia at traumatic brain injury?

A. Decreased apoptosis
B. Improved Glasgow Outcome Scale
C. Sweating
D. Pneumonia
E. Increased blood brain barrier permeability

Question 3

How soon after traumatic brain injury should therapeutic hypothermia be initiated?

A. Nobody knows for sure
B. Six hours
C. Seven days
D. Five weeks
E. A and B

Question 4

Which type of brain injury can be positively affected by therapeutic hypothermia?

A. Primary
B. Secondary
C. Tertiary
D. Quaternary

Question 5

What target temperature is least beneficial for therapeutic hypothermia at traumatic brain injury?

A. 33’ C
B. 33’ - 35’ C
C. 37’ C
D. 38.5’ C

References

1. Ahmed, A., et al. “Hypothermia in Traumatic Brain Injury.” *Neurosurgery Clinics of North America*. 27: 489-497. 2016.
2. Andrews, P., et al. “Targeted temperature management in patients with intracerebral hemorrhage, or acute ischemic stroke: consensus recommendations.” *British Journal of Anesthesia*. 121(4): 768-775. 2018.
3. Aminoff, M., et al. “Management of acute moderate and severe traumatic brain injury.” *UpToDate*. 2021.
4. Cook, C. “Induced Hypothermia in Neurocritical Care: A Review.” *Journal of Neuroscience Nursing*. 49(1): 5-11. 2017.
5. Cooper, D., et al. “Effect of Early Sustained Prophylactic Hypothermia on Neurologic Outcomes Among Patients with Severe Traumatic Brain Injury: The POLAR Randomized Clinical Trial.” *JAMA*. 320(21): 2211-2220. 2018.
6. Crompton, E., et al. “Meta-Analysis of Therapeutic Hypothermia for Traumatic Brain Injury in Adult and Pediatric Patients.” *Critical Care Medicine*. 45(4): 575-583. 2017.
7. Dietrich, W. and H. Bramlett. “Therapeutic hypothermia and Targeted Temperature Management in Traumatic Brain Injury: Clinical Challenges for Successful Translation.” *Brain Research*. 1640(PtA): 94-103. 2016.
8. Dietrich, W. and H. Bramlett. “Therapeutic hypothermia and targeted temperature management for traumatic brain injury: Experimental and clinical experience.” *Brain Circulation*. 3(4): 186-198. 2017.
9. Jain, A., et al. “Shivering Treatments for Targeted Temperature Management: A Review.” *Journal of Neuroscience Nursing*. 50(2): 63-67. 2018.
10. Lewis, S., et al. “Hypothermia for traumatic brain injury (Review).” *Cochrane Database of Systemic Reviews*. 9. 2017.
11. Madden, L. and H. DeVon. “Systematic Review of the Effects of Body Temperature on Outcome Following Adult Traumatic Brain Injury.” *Journal of Neuroscience Nursing.* 47(4): 190-203. 2015.
12. Madden, L., et al. “The Implementation of Targeted Temperature Management: An Evidence-Based Guideline from the Neurocritical Care Society.” *Neurocritical Care*. 27(3): 468-487. 2017.
13. Yokobori, S. and H. Yokota. “Targeted temperature management in traumatic brain injury.” *Journal of Intensive Care*. 4(28). 2016.