Krishna Dummula, MD
Neonatologist
The University of Kansas
Health System/Children's Mercy Kansas City

1

Children's Mercy

KU SCHOOL OF MEDICINE
The University of Kansas

Therapeutic Hypothermia

Krishna Dummula, MD

Review the guidelines for neuroprotective hypothermia in neonates
Discuss the results of recently published therapeutic hypothermia studies
Discuss clinical outcomes for infant undergoing therapeutic hypothermia for HIE

2

Disclosures: I have nothing to disclose

3

Therapeutic Hypothermia: Lingering questions at the bedside

- How quickly should we be getting babies down to goal temp once the decision has been made to cool?
  - Why is this the goal?
- What makes 72hrs of hypothermia therapeutic...why not longer or shorter?
- As a nurse, I don't know if I fully understand the cooling criteria - maybe this could be reviewed?
- How do I recognize an abnormal aEEG? What should I be reporting to the providers?
- Are there any adverse effects of passively cooling a baby; infant getting cold in the waiting period, and then we decide not to cool?

4

Classical Treatment of HIE

- Normothermia
- Control of Seizures
- Control of brain edema
- Maintenance of adequate ventilation
- Maintenance of optimal brain and organ perfusion
- Maintenance of normal metabolic status

5

Death and disability in HIE without Therapeutic Hypothermia

Outcome	Incidence	
Death	35%	(229/652)
Major Disability	38.6%	(159/411)
Cerebral Palsy	31.2%	(127/406)
Developmental Delay	34.7%	(126/363)
Blindness	10%	(33/329)
Deafness	5.8%	(18/312)

Table derived from: Tagin et al. Hypothermia for Neonatal Hypoxic Ischemic Encephalopathy: An Updated Systematic Review and Meta-analysis. Arch Pediatr Adolesc Med. 2012;166(6):558-566.

6

ACOG Consensus – 2014

- Neonatal signs consistent with an acute peripartum or intrapartum event:
  - Apgar score of less than 5 at 5 minutes and 10 minutes
  - Fetal umbilical artery pH<7.0, or base deficit ≥ 12 mmol/L, or both
  - Acute brain injury seen on brain MRI or MRS consistent with hypoxia ischemia
  - Presence of multisystem organ failure consistent with hypoxic-ischemic encephalopathy
- Contributing factors with an acute peripartum or intrapartum event
  - A sentinel hypoxic or ischemic event occurring immediately before or during labor and delivery
  - Fetal heart rate monitor patterns consistent with an acute peripartum or intrapartum event
  - No evidence of other proximal or distal factors that could be contributing
- Developmental outcome is spastic quadriplegia or dyskinetic cerebral palsy

Executive summary: Neonatal encephalopathy and neurologic outcome, second edition. Report of the American College of Obstetricians and Gynecologists' Task Force on Neonatal Encephalopathy. Obstet Gynecol. 2014 Apr;123(4):896-901.

7

AAP Guidance, 2014
Hypothermia and Neonatal Encephalopathy

- Moderate hypothermia (33.5-34.5 C) initiated within 6 hours after birth; continued for 72 hours followed by slow rewarming at 0.5 C/hr
- Eligibility criteria include:
  1. Gestational age ≥36 weeks and ≤6 hours of age
  2. A pH of ≤7.0 or a base deficit of ≥16 mmol/L in a sample of umbilical cord blood or blood obtained during the first hour after birth
  3. History of an acute perinatal event
  4. 10-minute Apgar score of of <5, or assisted ventilation initiated at birth and continued for at least 10 minutes
  5. In addition, a neurologic examination demonstrating moderate to severe encephalopathy is essential

Committee on Fetus and Newborn. Hypothermia and Neonatal Encephalopathy. Pediatrics June 2014, 133 (6) 1146-1150

8

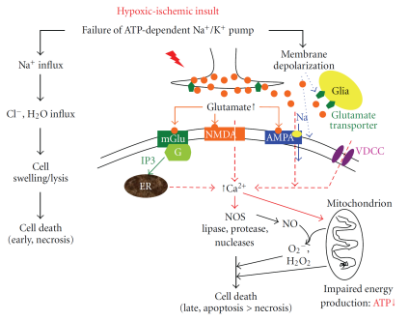
Neuromotor manifestations
Sarnat Score

Stage	Stage 1	Stage 2	Stage 3
Level of Consciousness	Hyperalert	Lethargic or obtunded	Stupor or coma
Activity	Normal	Decreased	Absent
Neuromuscular Control			
Muscle Tone	Normal	Mild hypotonia	Flaccid
Posture	Mild distal flexion	Strong distal flexion	Intermittent decerebration (extension)
Stretch Reflexes	Overactive	Overactive	Decreased or absent
Complex/Primitive Reflexes			
Suck	Weak	Weak or absent	Absent
Moro	Strong, low threshold	Weak, incomplete, high threshold	Absent
Tonic Neck	Slight	Strong	Absent
Autonomic Function			
Pupils	Mydriasis	Miosis	Variable, often unequal, poor light reflex, fixed, dilated
Heart Rate	Tachycardia	Bradycardia	Variable
Seizures	None	Common, focal or multifocal	Uncommon (excluding decerebration)

Sarnat H.B., Sarnat M.S. Neonatal encephalopathy following fetal distress. Arch Neurol.1976; 33:698-705.

9

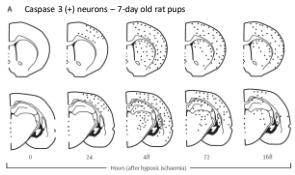
Mechanism of Injury in HIE



Lai MC, Yang SN. Perinatal Hypoxic-Ischemic Encephalopathy. J Biomed Biotechnol. 2011;2011:609813

10

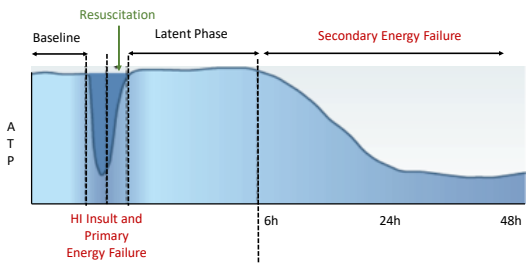
Neurons continue to commit to programmed cell death several days after injury



Nakajima et al. Apoptosis has a prolonged role in the neurodegeneration after hypoxic ischemia in the newborn rat. J Neurosci. 2000 Nov 1;20(21):7994-8004 [in] Johnston et al. Treatment advances in neonatal neuro-protection and neuro-intensive care. Lancet Neurol 2011; 10: 372–82

11

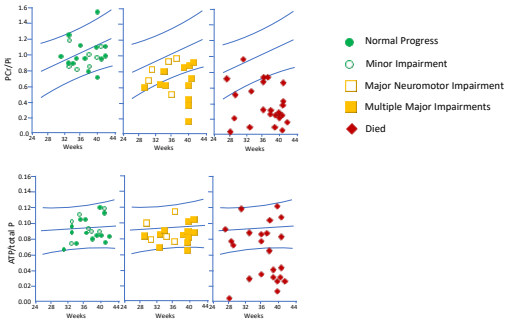
Energy failure paradigm in HIE



Thomas N. Therapeutic Hypothermia – Mechanisms of Action. In. Rennie JM, editor. Rennie and Roberton's Textbook of Neonatology. 5th Ed. Churchill Livingstone; 2012.p.1102-55

12

Energy failure in HIE is associated with poorer neurodevelopmental outcome



Azzopardi et al., Prognosis of newborn infants with hypoxic-ischemic brain injury assessed by phosphorus magnetic resonance spectroscopy. Pediatr Res. 1989 May;25(5):445-51.

13

Summary

- Neuronal cell death in HIE is predominantly apoptotic
- Cellular energy recovers temporarily after establishing reperfusion, only to secondarily deteriorate hours later, in a phase that may extend over many days
- Close correlation between the degree of delayed energy failure and neuro-developmental impairment in infants affected with HIE
- The latent period between primary energy failure and secondary energy failure creates a clear therapeutic window of opportunity to suppress/ameliorate cellular injury sequences which could potentially result in neuroprotection

14

Evolution of Therapeutic Hypothermia in Neonates

YEAR PLACE	MILESTONES
1983 UCL, London	MR Spectroscopy in infants lead to direct **study of energy metabolism in human brain**
1984 UCL, London	○ Concept of **delayed neuronal injury and secondary energy failure**. ○ **Potential window** for neuro-protective therapy was observed.
1995 UCL, London	**Hypothermia reduced secondary energy failure** following hypoxic brain injury in a piglet model when administered within the window period
1998 New Zealand	○ 1st pilot randomized control trial of therapeutic hypothermia in 31 newborn infants with HIE. ○ **Demonstration of the proof of principle, feasibility.** This was followed by 4 other pilot trials from US, Australia, Turkey and China
2005 US, UK, Australia, New Zealand	○ Three separate **multicenter randomized control trials** in therapeutic hypothermia (2-Whole body, 1-Selective head cooling) ○ Both whole body cooling trials showed significant reduction in the primary outcome (death and disability). ○ No risk reduction was seen with selective head cooling
2007	○ Three independent meta-analyses, including a Cochrane review showed significant reduction in death and long adverse neurodevelopmental outcome ○ Recruitment into the 3 ongoing therapeutic hypothermia trials became difficult.

Thayyil et al. Therapeutic Hypothermia for Neonatal Encephalopathy: Implications for Neonatal Units in India. Indian Pediatrics 2009: 46(17);283-289

15

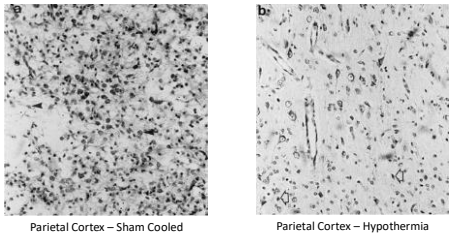
Therapeutic Hypothermia - Mechanism of Action

Phase	Effect
Acute Phase	Preservation of energy stores Reduction of excitatory amino acids
Sub-acute Phase	Prevention of apoptotic death Inhibition of Inflammation Reduction of BBB disruption
Chronic Phase	Enhanced differentiation of precursor cells Enhanced angiogenesis

Yenari MA, Han HS. Neuroprotective mechanisms of hypothermia in brain ischaemia. Nat Rev Neurosci. 2012 Feb 22;13(4):267-78

16

Hypothermia preserved neural cyto-architecture after hypoxia-ischemia in fetal lambs



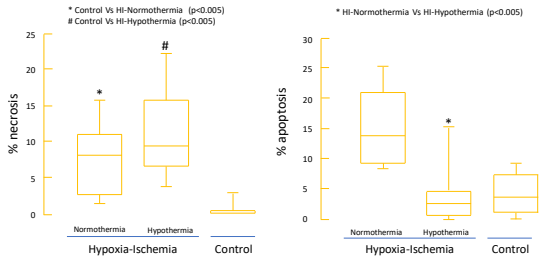
Parietal Cortex – Sham Cooled

Parietal Cortex – Hypothermia

Gunn et al. Dramatic neuronal rescue with prolonged selective head cooling after ischemia in fetal lambs. J Clin Invest. 1997 Jan 15;99(2):248-56.

17

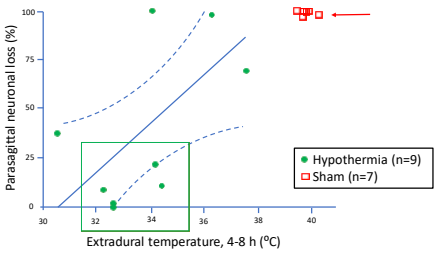
Hypothermia affords protection against apoptotic cell death and not necrosis



Edwards et al. Specific inhibition of apoptosis after cerebral hypoxia-ischaemia by moderate post-insult hypothermia. Biochem Biophys Res Commun. 1995 Dec 26;217(3):1193-9.

18

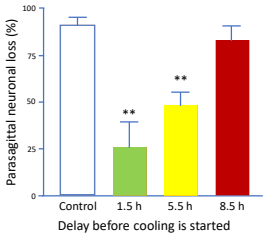
Ideal temperature window for therapeutic hypothermia



Gunn AJ, Gunn TR. The 'pharmacology' of neuronal rescue with cerebral hypothermia. Early Hum Dev. 1998 Nov;53(1):19-35.

19

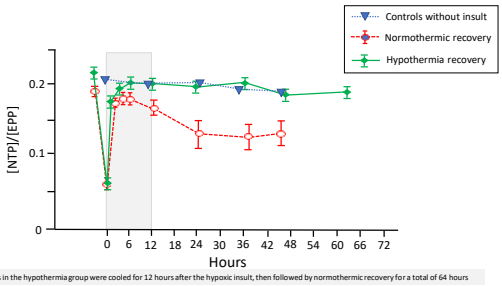
Initiation of therapeutic hypothermia beyond 6 hours is not beneficial



Gunn AJ and Bennet L. Neonatal Asphyxia. (2005). In FA Tisherman (ed) and P Sterz (ed), Therapeutic Hypothermia. 1st edn. pg. 141, New York, USA: Springer Science

20

Hypothermia mitigates delayed energy failure



Animals in the hypothermia group were cooled for 12 hours after the hypoxic insult, then followed by normothermic recovery for a total of 64 hours

Thoresen et al. Mild hypothermia after severe transient hypoxia-ischemia ameliorates delayed cerebral energy failure in the newborn piglet. Pediatr Res. 1995 May;37(5):667-70.in, Gunn and Thoresen, Neonatal encephalopathy and hypoxic-ischemic encephalopathy. Handbook of clinical neurology, Neonatal Neurology, Vol. 162 (3rd series); pp: 217-237.

21

Summary

- Mild hypothermia is neuro-protective
- Primarily benefits by preventing delayed (apoptotic) cell death
- Efficacious when started within 6 hours after birth
- Goal – Core temperature: 33-34 °C
- Long term cooling (72 hours) is more efficacious than short term cooling (6-12 hours)
- Rapid re-warming may be harmful

22

Moderate and severe injury groups are the primary focus of HIE therapies

	PROPORTION SEVERELY ABNORMAL OR DEAD (%)				
Study	N	Mild	Moderate	Severe	Duration of Follow-up (Yr)
Sarnat and Sarnat	21	–	25	100	1
Finer, et al	89	0	15	92	3.5
Robertson and Finer	200	0	27	100	3.5
Low, et al	42	–*	27	50	1
Levene, et al	122	1[†]	25	75	2.5

† Disability due to congenital myopathy.
* Mild and moderate considered together.

Martin, R. J., Fanaroff, A. A., & Walsh, M. C. (2011). Fanaroff and Martin's neonatal-perinatal medicine: Diseases of the fetus and infant (9th ed.). St. Louis, Mo.: Mosby/Elsevier.

23

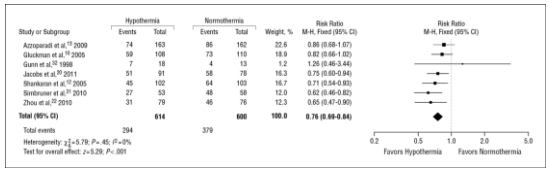
Initial hypothermia clinical studies used similar entry / cooling criteria

Clinical Studies	Entry Criteria
COOL CAP TRIAL Gluckman et al, 2005 Head Cooling 34-35 C for 72 hours	GA ≥ 36 weeks Apgar ≤ 5 at 10 min Or continued resuscitation at 10 min Or pH < 7.00 Or BD ≥ 16 mmol/L HIE grade 2 or 3 aEEG abnormalities
NICHD TRIAL Shankaran et al, 2005 Cooling Blanket 33-34 C for 72 hours	Acute perinatal event pH ≤ 7.0 or BD ≥ 16 mmol/L Apgar ≤ 5 at 10 min IPPV ≥ 10 min Encephalopathy or seizures
TOBY TRIAL Azzopardi et al, 2009 Cooling Mattress 33.5 ± 0.5 C for 72 hours	One of: Apgar ≤ 5 at 10 min Resuscitation for ≥ 10 min pH < 7.0 or BD ≥ 16 mmol/L at 60 min and HIE grade 2 or 3 and aEEG abnormalities
ICE TRIAL Jacobs et al, 2011 Refrigerated Gel Packs 33-34 C for 72 hours	Evidence of moderate to severe encephalopathy + At least 2 of the following: Apgar ≤ 5 at 10 min IPPV at 10 minutes PH < 7.0 or BD ≥ 12 mmol/L within 60 min of birth

24

Meta-analyses of published studies favor use of therapeutic hypothermia

Composite primary outcome of death or major disability in survivors

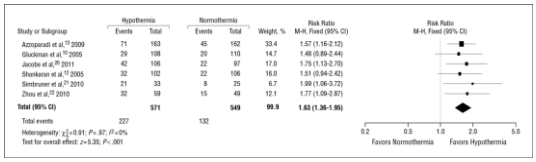


Diamond indicates overall summary estimate for the analysis (width of the diamond represents the 95% CI).
M-H indicates Mantel-Haenzel test.

Tagin et al. Hypothermia for Neonatal Hypoxic Ischemic Encephalopathy: An Updated Systematic Review and Meta-analysis. Arch Pediatr Adolesc Med. 2012;166(6):558-566.

25

Therapeutic hypothermia enhances intact neurologic outcome in infants born with HIE



Diamond indicates overall summary estimate for the analysis (width of the diamond represents the 95% CI).
M-H indicates Mantel-Haenzel test.

Tagin et al. Hypothermia for Neonatal Hypoxic Ischemic Encephalopathy: An Updated Systematic Review and Meta-analysis. Arch Pediatr Adolesc Med. 2012;166(6):558-566.

26

Hypothermia benefits are sustained through early childhood (6-7 years)

NICHD Whole Body Cooling: 91% follow-up at 6-7 years of age

Outcome measure	Hypothermia group	Control group	Relative risk (95% CI)	P-value
Combined outcome of death or IQ score < 70	47%	62%	0.78 (0.61-1.01)	0.06
Death alone	28%	44%	0.66 (0.45-0.97)	0.04
Risk of death or severe disability	41%	60%	0.72 (0.54-0.97)	0.03

Shankaran et al. Childhood outcomes after hypothermia for neonatal encephalopathy. N Engl J Med. 2012 May 31;366(22):2085-92.

27

Is it possible to further optimize therapeutic hypothermia?

STARTING SOONER:

- Delaying initiation of cooling dramatically reduces its neuroprotective efficacy in animal studies
- Thoresen et al, 2013:
  - Cooling started before 3 hours of age had significantly better psychomotor development index (PDI) scores Vs those who were cooled after 3 hours of age
- Sankaran et al, 2017:
  - Rate of death or disability improved to 29.3% versus 44% in previous (2005) trial by the same group
  - Improvement is speculatively attributed to earlier initiation of cooling

1. Shankaran et al. Effect of depth and duration of cooling on death or disability at age 18 months among neonates with hypoxic-ischemic encephalopathy. A randomized clinical trial. JAMA 318(1): 57-67
2. Thoresen et al. Time is brain: starting therapeutic hypothermia within three hours after birth improves motor outcome in asphyxiated newborns. Neonatology. 2013; 104(3): 228-33
3. Wassink et al. Therapeutic hypothermia in neonatal hypoxic-ischemic encephalopathy. Current Neurology and Neuroscience Reports, 19(1), [2]

28

Is it possible to further optimize therapeutic hypothermia?

STARTING LATER:

- Delaying initiation of cooling dramatically reduces its neuroprotective efficacy in animal studies
- Laptook et al, 2017:
  - 168 term infants with HIE who couldn't be started on hypothermia within 6 hours
  - Randomized to hypothermia or normothermia between >6 and <24 hours (Median 16 h)
  - Neurodevelopmental outcome was assessed in survivors at 18-22 months with Bayley-III
  - Outcome was available for:
    - 78 cooled patients (9 died and 10 had moderate to severe disability)
    - 79 normothermic patients (9 died and 13 had moderate to severe disability)
  - Bayesian analysis suggested a 71, 64 or 56% probability of reducing death or disability by at least 1, 2 or 3% respectively
  - Summarily, the study shows uncertain efficacy of hypothermia if started after 6 hours

1. Laptook et al. Effect of therapeutic hypothermia initiated after 6 hours of age on death or disability among newborns with hypoxic-ischemic encephalopathy: A randomized clinical trial. JAMA 2017; 318(16):1550-60

29

Is it possible to further optimize therapeutic hypothermia?

DEEPER COOLING:

- Animal studies suggest cooling below 33.5 C is not associated with any additional neuroprotection
- Shankaran et al, 2017:
  - Large randomized clinical control trial
  - Evaluated if cooling deeper (32 C) or longer (120 hours) reduces death or disability
  - Trial was stopped for issues of safety and futility after recruiting half the projected numbers
  - Cooling infants with moderate to severe HIE to 32 C instead of 33.5 C did not further reduce death or moderate to severe disability at 18 months of age. Adjusted risk ratio - 1.24 (95% CI: 0.69-2.25)
  - Study concluded that a relatively broad range of temperatures are beneficial for the brain and it should not be necessary to reduce core temperatures by more than 3.5 C

1. Shankaran et al. Effect of depth and duration of cooling on death or disability at age 18 months among neonates with hypoxic-ischemic encephalopathy. A randomized clinical trial. JAMA 318(1): 57-67
2. Wassink et al. Therapeutic hypothermia in neonatal hypoxic-ischemic encephalopathy. Current Neurology and Neuroscience Reports, 19(1), [2]

30

Is it possible to further optimize therapeutic hypothermia?

DEEPER COOLING:

- Preclinical studies in sheep suggest that continuing hypothermia for 72 hours is needed for optimal neuroprotection
- Shankaran et al, 2017:
  - Large randomized clinical control trial
  - Evaluated if cooling deeper (32 C) or longer (120 hours) reduces death or disability
  - Trial was stopped for issues of safety and futility after recruiting half the projected numbers
  - Adjusted risk ratio for death in the neonatal intensive care unit after cooling for 120 hours compared to 72 hours was 1.37 (95% CI: 0.92-2.04).
  - No significant overall effect of longer cooling on death of disability was found at age 18 months

1. Wassink et al. Therapeutic hypothermia in neonatal hypoxic-ischemic encephalopathy. Current Neurology and Neuroscience Reports, 19(1), [2]
2. Davidson et al. How long is too long for cerebral cooling after ischemia in fetal sheep? J Cereb Blood Flow Metab. 2015;35(5):751-8
3. Shankaran et al. Effect of depth and duration of cooling on death or disability at age 18 months among neonates with hypoxic-ischemic encephalopathy. A randomized clinical trial. JAMA 316(1): 57-67

31

Is it possible to further optimize therapeutic hypothermia?

COOLING INFANTS WITH MILD HIE:

- Large RCTs of therapeutic hypothermia excluded infants with mild HIE due to unknown risk of adverse outcome
- Potential benefit of treating these infants with therapeutic hypothermia is unknown
- **Chalak et al, 2018**
  - Prospective cohort study of mild HIE
  - Study found 16% of infants had disability at a mean of 19 months
  - 40% of infants had Bayley scores more than one SD below the mean (< 85) for either cognition, motor, or language.
- **Murray et al, 2016**
  - Prospective cohort study of infants with mild HIE not treated with hypothermia
  - Infants with mild HIE had adverse cognitive and neuromotor outcomes at 5 years of age compared to healthy peers
  - Although intact survival was much greater after mild than moderate or severe HIE, survivors showed no significant difference in cognitive outcomes between those who had had mild compared to moderate HIE.
- **Randomized control trial in the offing**
  - TIME Study: Therapeutic Hypothermia for Infants with Mild Encephalopathy (TIME)
  - PI: Sonia Bonafacio, Stanford University (NCT04176471)

1. Wassink et al. Therapeutic hypothermia in neonatal hypoxic-ischemic encephalopathy. Current Neurology and Neuroscience Reports, 19(1), [2]
2. Chalak et al. Prospective research in infants with mild encephalopathy identified in the first six hours of life: neurodevelopmental outcomes at 18-22 months. Pediatr Res 2018 Dec;84(6):861-868.
3. Murray et al. Early EEG grade and outcome at 5 years after mild neonatal hypoxic ischemic encephalopathy. Pediatrics. 2016; 138(4)

32

Issues yet to be addressed To cool or not to cool?

Hypothermia treatment outside trial criteria:

- Apparently mild neonatal encephalopathy
- Gestation age < 36 weeks at birth
- Postnatal collapse
- Neonatal stroke
- Infants admitted with low arterial cord pH <7.0 who appear clinically well
- The encephalopathic infant whose clinical condition improves
  - Within 6 hours of birth
  - After 6 hours of birth
- The infant who develops 'rebound' seizures during or immediately following rewarming
- Infants in whom the diagnosis of HIE is uncertain

Austin et al. To cool or not to cool? Hypothermia treatment outside trial criteria. Arch Dis Child Fetal Neonatal Ed. 2013 Sep;98(5):F451-3.

33

In Summary

- Current protocols for therapeutic hypothermia are near optimal
- Earlier diagnosis and initiation of hypothermia may further improve neurodevelopmental outcomes after HIE
- Add-on therapies for therapeutic hypothermia may complement its beneficial effects in the future

34

Thank You

Krishna Dummula, MD

Whole Body Cooling

Selective Head Cooling

35