

## Hypoxic Ischemic Encephalopathy in the Neonate

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## Disclosures

- No relevant financial relationships or conflicts of interest to disclose
- Review therapies currently under research

## Objectives

- Definition
- Pathophysiology
- Treatment Strategies
  - Therapeutic Hypothermia
  - Emerging therapies in HIE

## Definition: HIE

- Hypoxia  
Decreased oxygen delivery to tissues
- Ischemia  
Decreased blood flow to tissues
- Encephalopathy  
Disturbed neurologic function

## HIE: Incidence

- Developed countries  
1 - 8 per 1000 live births
- Developing countries  
26 per 1000 live births

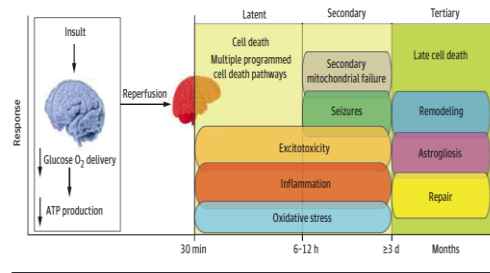
## Impact

- Major cause of encephalopathy in the neonatal period
- Large human and financial costs
  - Can lead to:
    - Death, cerebral palsy, epilepsy, cognitive, developmental and behavioral problems

## Pathophysiology of HIE

- Complex evolving process
- Initiate at time of initial insult
- Extends to recovery period

Figure 1. Schematic Overview of the Pathophysiological Features of Hypoxic-Ischemic Encephalopathy



Douglas-Escobar et al JAMA 2015

## Early Identification of at risk Newborns Nurses- Critical Role

- Evidence of acute perinatal insult
  - Indicated by:
    - Sentinel event
    - Delivery room resuscitation
    - 5 minute APGAR score ≤ 5
    - Cord arterial PH ≤ 7.0
- +
- Postnatal evidence of encephalopathy
  - Clinical
  - EEG

## Neurologic Evaluation Nurse- Critical Role

- Level of consciousness
- Neuromuscular control
- Reflexes
- Autonomic function
- Ongoing evaluation!!!

## HIE Severity- Sarnat

	Stage 1	Stage 2	Stage 3
Consciousness	Hyperalert	Lethargic / Obtunded	Stupor / Coma
Activity	Normal	Decreased	Absent
Neuromuscular Control - Muscle Tone - Posture - Stretch Reflexes	Normal Mild flexion Overactive	Mild hypotonia Strong distal flexion Overactive	Flaccid Intermittent decerebration Decreased/Absent
Primitive Reflexes - Suck - Moro - Tonic neck	Weak Strong Slight	Weak / Absent Weak/Incomplete Strong	Absent Absent Absent
Autonomic function - Pupils - Heart rate	Normal Tachycardia	Miosis Bradycardia	Mydriasis / Variable Variable
Seizures	None	Common	Uncommon

Sarnat. Arch Neurol 1976

## Laboratory

- Metabolic acidosis
  - Cord blood gas / Newborn blood gas
- Concomitant injury to other organs
  - Liver Elevated transaminases
  - Kidney: elevated creatinine
  - Heart: elevated CK-MB, troponin
  - Thrombocytopenia

## HIE: Sarnat Stages and Outcome Before Therapeutic Hypothermia

	Deaths	Neurologic Sequelae	Normal
Mild	0%	0%	100%
Moderate	5%	24%	71%
Severe	80%	20%	0%
All	13%	14%	73%

Robertson C, Finer N (1985) *Dev Med Child Neuro*  
 Thornberg et al (1995) *Acta Paediatr*

## Therapeutic Hypothermia

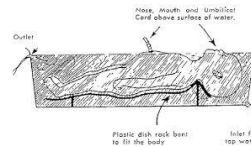


## History of Therapeutic Hypothermia

- 4<sup>th</sup>-5<sup>th</sup> century B.C. -Greece
  - Cold water for febrile convulsions
  - Minimize hemorrhage in the wounded
  - Treatment for tetanus
- 17<sup>th</sup> century -Russia
  - Covered people in snow in an attempt to resuscitate them
- 19<sup>th</sup> century- France
  - Anesthesia for amputations
- 20<sup>th</sup> century
  - Pain relief, tumor reduction, cardiac arrest

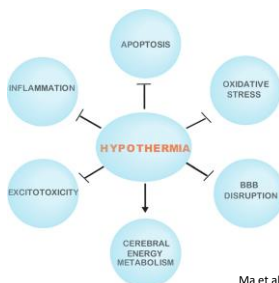
## History of Therapeutic Hypothermia in Newborns

- Immersion bath used to resuscitate and cool newborn infants who were unresponsive after 5 minutes. Infants were taken out of the cold bath when breathing resumed.



Westin et al  
 – Surgery 1959  
 – Acta Paediatr Scand 1962  
 – Am J Obstet Gynecol. 1971

## Therapeutic Hypothermia Mechanism



Ma et al *Curr Mol Med* 2012

## Where is the evidence?



## Animal Studies

- Cooling brain to 32-34°C starting within 5.5 hours of an HIE insult and continuing to cool for 12-72 hours resulted in improved neuropathologic and functional outcomes.
- EEG dramatically improved
- Systemic toxicity not a major issue

Gunn et al. Early Hum Dev. 1988  
Thoreson et al. 1996 Arch Dis Child

## Preliminary Clinical Trials

- Small safety, feasibility, practicality studies.
- Reducing body temperature by 2 - 3°C for a prolonged period of time – possible.
- Changes in vital signs - Little clinical significance.

Gunn Pediatrics 1998  
Azzopardi Pediatrics 2000  
Gebauer Pediatrics 2006

## Large Randomized Clinical Trials

- 6 RCT published between 2005- 2011
- Variation in criteria but for all :
  - > 35 weeks of gestation
  - Randomized by 6 hours of age
  - Target temperature 33.5- 34.5C
  - 72 hour intervention period
  - Slow rewarming (0.5 °C/hour)
  - Primary outcome measure: Combined rate of death and disability assessed at 18-22 months.

## Therapeutic Hypothermia Randomized Clinical Trials

Study/year	Gest Age	Type	Temp (- C)	Duration (hours)
Azzopardi/TOBY '09	≥36	WBC	33-34 (rectal)	72
Jacobs/ICE '11	≥35	WBC	33-34 (rectal)	72
Shankaran/NICHD '05, '12	≥36	WBC	33.5 (esophageal)	72
Simbruner/nEURO '10	≥36	WBC	33.5 (rectal)	72
Gluckman/CoolCap '05, '12	≥36	SHC	34-35 (rectal)	72
Zhou '10	≥36	SHC	34 (nasopharyngeal)	72

WBC= whole body cooling, SHC= selective head cooling

Allen Advances in Neonatal Care 2014

## Therapeutic Hypothermia Meta-Analysis

- Reduces risk of death or major neurodevelopmental disability
- Increases the rate of normal neurologic survival at 18 months

Tagin MA Arch Pediatr Adolesc Med. 2012

## Cochrane Review 2013

- 11 Randomized Controlled Trials
- Therapeutic hypothermia is beneficial in term and late preterm newborns with moderate to severe HIE

Reduction in Death / Major neurodevelopmental disability at 18 months for infants treated with hypothermia

Overall (Moderate + Severe HIE)	25%
Moderate HIE	32%
Severe HIE	18%

Jacobs Cochrane 2013

## Cochrane Review 2013

- Benefits outweigh short-term adverse effects
- Should be instituted in term and late preterm infants with moderate to severe HIE within 6 hours of age.

Jacobs Cochrane 2013

## Therapeutic Hypothermia Long-term Trial Outcomes

Study/year	Age (years)	Primary Outcome	Result/Conclusion
NICHD Whole Body Cooling	6-7	Death or an IQ <70	47% (hypothermia) vs. 62% (controls) (P=0.06) *Lower death rate and no increase in disability
CoolCap Selective Head Cooling	7-8	Determine if 18mo neurodevelopmental outcomes predict functional outcome at age 7-8 years	No significant difference in functional independence between hypothermia vs. controls

Allen KA. Advances in Neonatal Care 2014

## Therapeutic Hypothermia Adverse effects

- Sinus bradycardia
- Prolongation of QT interval
- Reddening / Hardening of skin
- Subcutaneous fat necrosis- Rare
- Thrombocytopenia

## Seizures

- Increase the metabolic demand within the brain
- May be subtle and only seen on EEG
  - Nurse critical role!
- Phenobarbital –Most common drug
- Keppra -Recommended for additional control

## Transport & Therapeutic Hypothermia

- 1/3 of babies with HIE admitted to NICU at > 6 hours of age.

Vermont Oxford Network

- ? Therapeutic Hypothermia on transport
  - Passive
    - Ice packs
  - Active
    - Servo controlled device

## Therapeutic Hypothermia & Transport

- Canada: 44% of patients had temperatures <33°C
- ICE Trial: Multicenter, international RCT (2001-2007)
  - Passive cooling or active cooling with gel packs
  - Hypothermia:
    - 56.4% -At least one temperature measurement of 29.8-32.9 °C
- California: Therapeutic Hypothermia during neonatal transport
  - 87% - passive cooling.
  - > 50% of infant's cooled on transport do not achieve target temperature

### -Conclusion

Difficult to achieve "target" temperature with passive cooling / non-device active cooling

Kurshid et al. Paediatr Child Health 2011  
Jacobs et al Arch Pediatr Adolesc Med 2011  
Akula et al Journal of Perinatology 2013

### Therapeutic Hypothermia Device for Transport Tecotherm®



- Studied on transport
- FDA approved

### Therapeutic Hypothermia on Transport Servo-controlled device

Table III. Primary, secondary, and neonatal outcomes

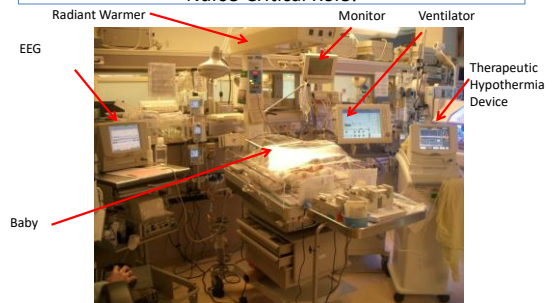
Outcomes	Device (N = 51), n (%)	Control (N = 49), n (%)	P value
<b>Primary outcome</b>			
Temperatures in target range during transport (%) <sup>a</sup>	73 (17-88)	0 (0-52)	<.001
<b>Secondary outcomes</b>			
Subjects in target temperature anytime during transport	41 (80)	24 (49)	<.001
Time to target temperature (min) <sup>b</sup>	44 ± 31	63 ± 37	.04
Subjects in target range at 60 min <sup>c</sup>	28 (71)	8 (20)	<.001
<b>Neonatal outcomes</b>			
Length of ventilation (d) <sup>d,e</sup>	3.9 ± 3	3.2 ± 3	.42
Length of hospitalization (d) <sup>f,g</sup>	13.9 ± 9.1	13.4 ± 9.6	.85
Inhaled nitric oxide use	12 (23)	5 (10)	.11
ECMO use	1 (2)	0 (0)	1.00
Mortality <sup>h</sup>	9 (18)	6 (12)	.44

- **Conclusion:** TH using a servo-regulated device provides more predictable temperature management during neonatal transport for out-born newborns with neonatal encephalopathy.

### HIE: Other management strategies

- Supportive Care
  - Cardiorespiratory Support
  - Fluid Management
  - Glucose control
  - Multiorgan Failure
  - Seizure Management
  - EEG & Imaging
  - Family Support
  - Follow-up

### Supportive Care Nurse-Critical Role!



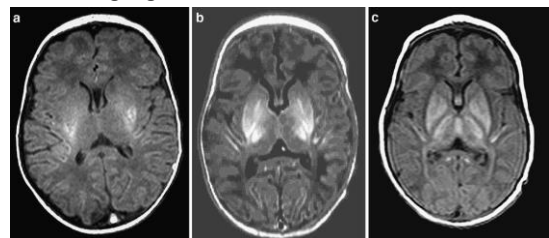
Etc....etc.....

### Neuroimaging

- MRI with Diffusion-Weighted Imaging
- MR Spectroscopy
  - Deep gray matter, white matter
  - Increased lactate and decreased N-acetyl-aspartate (NAA) peak → severe tissue injury
- MRI interpretation in the neonate is difficult
  - -Need an expert in pediatric neuroradiology

### MRI

- Basal ganglia and Thalamus



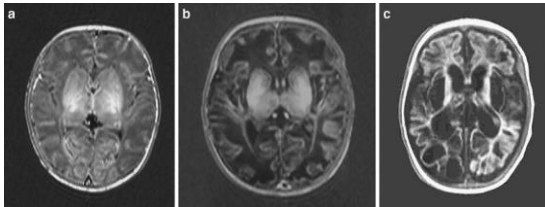
MILD

MODERATE

SEVERE

## MRI

- Severe injury over time



4 DAYS

8 DAYS

3 MONTHS

## Need for adjuvant therapies

- Despite the use of therapeutic hypothermia for neonatal HIE, incidence of death and disability remains high after treatment with therapeutic hypothermia

– Approximately 40%

Papile. Pediatrics 2014

## Adjuvant Therapies

- Promising neuroprotective agents
  - Antiepileptic drugs
  - Erythropoietin
    - Animal data: Neuroprotective, safe
      - Ongoing clinical trial
  - Melatonin
    - Animal data: EPO + Melatonin: Improved neurologic outcome
  - Xenon

Wu Developmental Medicine and Child Neuro 2015  
Jantzie Front Neurol.

## Areas of uncertainty Trials

- Therapeutic hypothermia for mild HIE
- Therapeutic hypothermia initiated after 6 hours of age
- Depth of hypothermia
- Duration of therapy
- Therapeutic hypothermia for <35 week gestation newborns

## Therapeutic Hypothermia for Mild HIE ?

- Neurologic evaluation is subjective
- Timing of insult affects clinical presentation
- Many centers have shifted from published protocols and consider therapeutic hypothermia for mild HIE
- Need a randomized controlled trial

Chalack Early Human Development 2018

## Therapeutic Hypothermia after 6 hours?

- Multicenter RCT
- TH initiated 6-24 hours after birth
- >36 week gestation with moderate- severe HIE
  - Randomized to TH or no TH
- Main outcome: Composite death or moderate to severe disability at 18-22 months
- Results: TH at 6-24 hours compared to no TH resulted in:
  - 76% probability of any reduction in death or disability
  - 64% probability of at least 2% less death or disability at 18-22 months
- Conclusion: TH initiated at 6-24 hours after birth may have benefit but there is uncertainty about its effectiveness.

Laptook JAMA 2017

## Different depth and duration of therapeutic hypothermia ?

- Previous trials looked at 72 hours of cooling
- Animal model: Longer, Deeper cooling-Neuroprotective
- Randomized controlled trial
  - Longer cooling (120 hours)+ Deeper cooling (32°C) compared to
    - Standard (72 hours, 33.5°C)
- Primary Outcome: Death or disability at 18-22 months
- Results:
  - No difference in NICU death
  - Cooling for 120 hours to lower than 33.5°C did not reduce death or moderate to severe disability at 18-22 months
    - Underpowered

Shankaran et al JAMA

## ? Therapeutic Hypothermia for Premature Newborns

- Ongoing trial
  - NCT: 1793129
- 33 to 35 week gestation age
- No results yet

## Conclusions

- Therapeutic hypothermia is standard of care for newborns >35 weeks of gestation with moderate to severe hypoxic ischemic encephalopathy
- Survivors are at risk for long-term neurodevelopmental disability
- Adjuvant therapies are needed and are currently under investigation.
- Medical centers offering hypothermia should be capable of providing comprehensive clinical care including neuroimaging, neurologic consultation and follow up.

Thank you

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