

NEUROPROTECTION IN THE NEONATE

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 April 19, 2012

Objectives

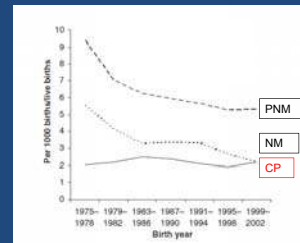
- Perinatal brain injury
- Neuroprotection in the neonate
 - Preterm
 - Term

Perinatal Brain Injury

- Important cause of DEATH and DISABILITY
- Lifetime
- Improvement in perinatal and neonatal care
 - Improved survival
 - No significant ↓ in neurologic disabilities

Perinatal Brain Injury

Perinatal, Neonatal Mortality and Cerebral Palsy (Sweden), 1975-2002



Himmelman (2010) Acta Paediatrica

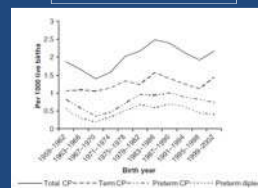
Perinatal Brain Injury

- No effective TREATMENT for perinatal brain lesions
- NEUROPROTECTIVE strategies
 - Cerebral Palsy
 - Cognitive Impairment
 - Others

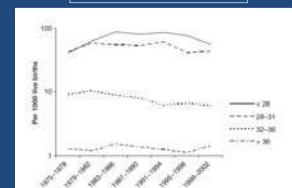
Cerebral Palsy (CP)

- Motor impairment due to malformation/lesion in the immature brain
- Often accompanying impairments
 - Cognition, communication, sensation

CP Prevalence, 1959-2002



CP by Gestational Age



Himmelman (2010) Acta Paediatrica

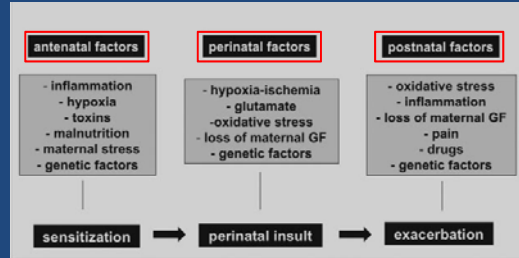
Pathophysiology

- Periventricular white matter injury
 - Generally, <32weeks
- Cortical and subcortical lesions
 - Term



Pathophysiology - PRETERM

- MULTIfactorial



Preterm Neuroprotection

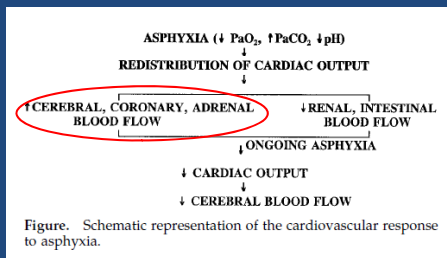
- Antenatal
 - Magnesium
 - Antenatal steroids
- Neonatal
 - ? Caffeine
 - X Indomethacin
 - X Vitamin A

Brain Injury in the Term Infant

- Stroke
- Birth trauma
- Metabolic or genetic disorders
- **Hypoxic ischemic encephalopathy (HIE)**
 - One of the most commonly recognized causes of severe, long-term neurologic deficits in children
 - Death, cerebral palsy, epilepsy, cognitive, developmental and behavioral problems
 - Incidence: ~1.5 per 1000 live births
 - Large human and financial costs

Fetal Response - Circulatory

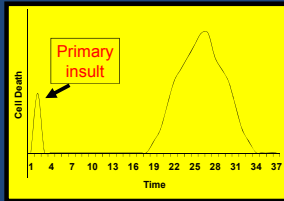
- Interruptions in placental blood flow is common BUT neurologic sequelae are infrequent



Perinatal HIE

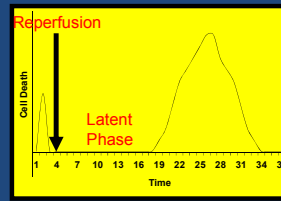
- Evolving process
 - 1° energy failure during asphyxia
 - **Necrosis**
 - Precipitates a biochemical cascade
 - Latent phase lasting 6–24 hr
 - 2° energy failure leads to most of the cell death
 - **Apoptosis**
- Severity of **2° energy failure** is correlated with adverse neurodevelopmental outcome

HIE: Primary Insult



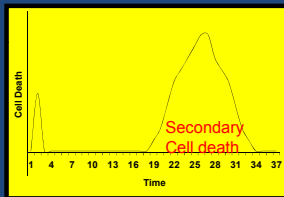
- **Primary insult**
 - High energy metabolites depleted (energy failure)
 - Swelling
 - Accumulation of excitatory amino acids
 - Cell necrosis

HIE: Latent Phase



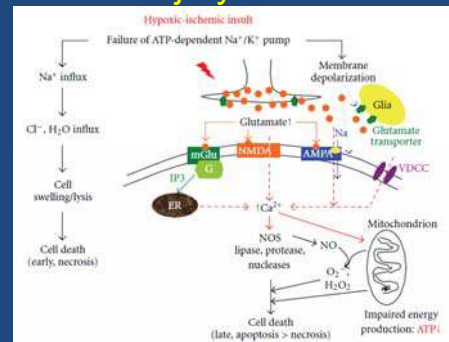
- **Latent phase (6-15h)**
 - Cerebral circulation and oxygenation restored
 - Cerebral oxidative metabolism normalized
 - Depressed EEG
 - Decreased cerebral blood flow

HIE: Secondary Energy Failure



- **Secondary energy failure (1-10 days)**
 - Delayed seizures
 - Cell swelling
 - Excitotoxin accumulation
 - Mitochondrial failure
 - Cell death (apoptosis)

HIE Injury Cascade



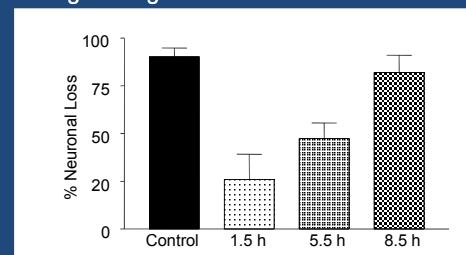
Lai (2010) J Biomed and Biotech

Stopping the Injury Cascade



Therapeutic Hypothermia

- Effect of delay after cerebral ischemia before starting cooling



Gunn et al JCI 1997;99:248-58; Gunn et al. Ped 1998;102:1098-106; Gunn et al Pediatr Res 1999;46:274-80

Hypothermia

- Whole Body Cooling or Head Cooling
- Halts 2° cell death
- Low toxicity
- Hypothermia protected **animal** models subjected to asphyxia
 - Cooling within 6 hr (**earliest best**)
 - >24 hr of cooling (**72 hr is better**)
 - Brain surface needs to be cooled to **<34°C**

Supportive Care

Radiant Warmer
Monitor
Ventilator
Baby
aEEG
Cool Cap

Therapeutic Hypothermia

- Outcomes up to 18 months

Study	Hypothermia		Normothermia		Neonatal Hypothermia	
	Total	Events	Total	Events	Relative Risk	95% CI
CoolCap	198	28	142	38	1.68	0.82 - 3.02
NOHA	102	32	106	32	1.81	0.94 - 3.45
TOBY	163	71	162	45	1.87	1.16 - 3.02
Combined	463	131	410	115	1.93	1.23 - 3.05

Roka A (2010) *Early Human Dev*

Cool Cap

- Arkansas Children's Hospital (ACH) participated in the Cool Cap Trial
- FDA approved Olympic Cool Cap® on 12/20/06 with specific enrollment criteria
- Core (rectal) temp at 34.5°C ± 0.5°C for 72 hrs

Enrollment Criteria: A + B + C

A. GA≥36wks + at least one (1)

- Apgar ≤5 at 10min
- Continued need for resuscitation, including ET or bagging at 10min
- Acidosis: pH <7 (umbilical cord pH or any arterial pH within 60 minutes of birth)
- BD≥16 mmol/L in any blood sample within 60min of birth

B. Moderate to Severe Encephalopathy consisting of altered state of consciousness (as shown by lethargy, stupor or coma) and at least one of the following:

- Hypotonia
- Abnormal reflexes, including oculomotor or papillary abnormalities
- Absent or weak suck
- Clinical seizures

C. aEEG/CFM Recording of at least 20 minutes duration that shows either moderately or severely abnormal aEEG background (score of 2 or 3) or seizures

INITIATE HYPOTHERMIA BY SIX (6) HOURS OF BIRTH

IF IN DOUBT, CALL ACH ANGEL ONE ®

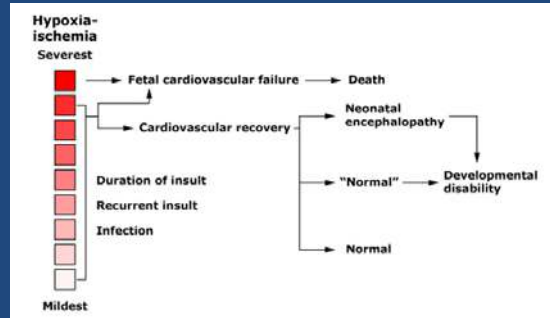
Toll Free: 1-800-ACH-HELP
(1-800-224-4357)
Direct Line: (501) 364-6429

Acute Intrapartum Event Sufficient to Cause CP (ACOG)

- **Essential Criteria (all 4)**
 - Metabolic acidosis in fetal arterial cord blood (pH<7, BD≥12)
 - Mod-severe neonatal enceph ≥34wks GA
 - Spastic quad or dyskinetic type CP
 - Excluding other etiologies
- **Intrapartum timing (“0-48H”)**
 - Sentinel event
 - Fetal heart tracing
 - Apgar 0-3 beyond 5 min
 - Multisystem involvement within 72H
 - Early imaging: nonfocal cerebral abnormality

ACOG, Committee on Obstetric Practice (2005)

HIE and Outcome



Long-Term Follow-Up

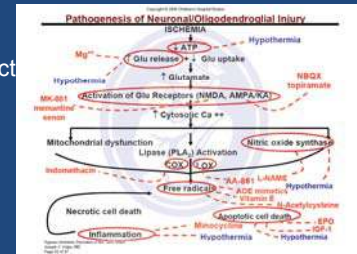
- >40% of infants who receive therapeutic hypothermia still have abnormal outcomes

Outcome	Hypothermia		Normothermia		Relative risk	95% CI start	95% CI end	P value
	Total	Events	Total	Events				
Death or disability	600	123	266	223	0.66	0.11	0.93	0.002
Death	600	109	266	217	0.78	0.06	0.91	0.005
Severe disability	270	76	250	99	0.71	0.56	0.91	0.006
Cerebral palsy	289	71	249	96	0.68	0.54	0.89	0.004
Psychomotor developmental index <70	260	68	233	86	0.71	0.54	0.92	0.02
Mental developmental index <70	251	68	222	82	0.73	0.56	0.92	0.01
Blindness	288	30	241	32	0.56	0.33	0.96	0.03

Main neurological outcomes to 18 months of age. For all outcomes studies are QUINCY (20) NICE (21) TROV (22). For rate of death additional studies included are: Akh (23), Shunkara (2002) (10), Ecker (15), Liu (14), Roberts (18), Jacobs (19), Sankaran (24).

Future Directions

- Interventions affecting multiple sites are required
- Hypothermia affects multiple sites
- Inhaled Xenon
- Erythropoietin
- N-acetylcysteine
- Melatonin
- Anticonvulsants



Conclusion

- Neuroprotection in term neonates
 - Hypothermia
 - Adjunct strategies – currently under study
- Neuroprotection in preterm neonates
 - Periventricular white matter injury
 - No proven strategies