

## NEUROPROTECTION IN THE NEONATE

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## Objectives

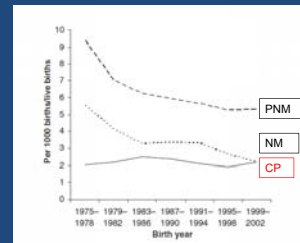
- Perinatal brain injury
- Neuroprotection in the neonate
  - Preterm
  - Term

## 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*

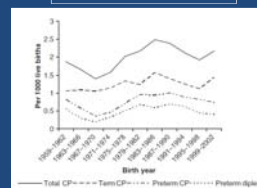
## Perinatal Brain Injury

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

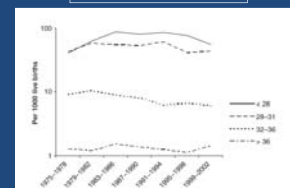
## Cerebral Palsy (CP)

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

CP Prevalence, 1959-2002



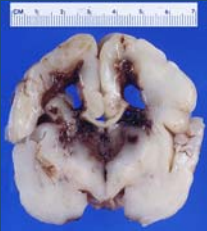
CP by Gestational Age



Himmelman (2010) *Acta Paediatrica*

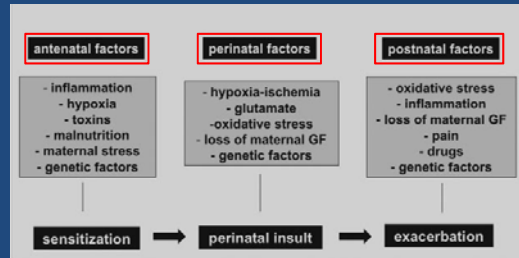
## Pathophysiology

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



## Pathophysiology - PRETERM

- MULTIfactorial



## Preterm Neuroprotection

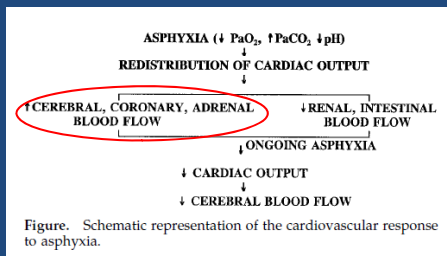
- Antenatal
  - Magnesium
  - Antenatal steroids
- Neonatal
  - ? Caffeine
  - X Indomethacin
  - X Vitamin A

## 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

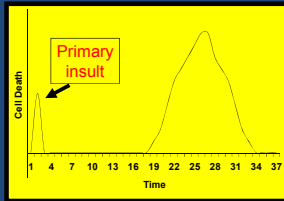
- Interruptions in placental blood flow is common BUT neurologic sequelae are infrequent



## Perinatal HIE

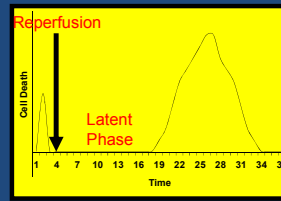
- Evolving process
  - 1° energy failure during asphyxia
    - **Necrosis**
  - Precipitates a biochemical cascade
  - Latent phase lasting 6–24 hr
  - 2° energy failure leads to most of the cell death
    - **Apoptosis**
- Severity of **2° energy failure** is correlated with adverse neurodevelopmental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

## HIE: Primary Insult



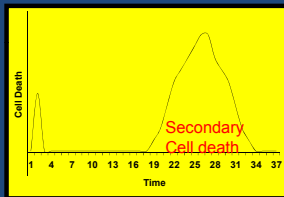
- **Primary insult**
  - High energy metabolites depleted (energy failure)
  - Swelling
  - Accumulation of excitatory amino acids
  - Cell necrosis

## HIE: Latent Phase



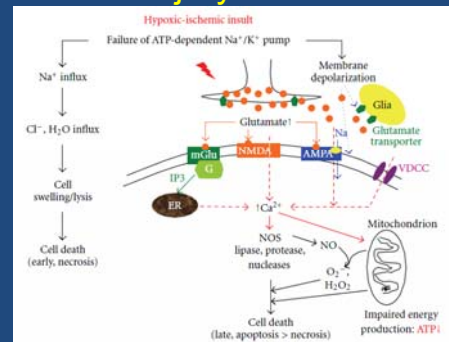
- **Latent phase (6-15h)**
  - Cerebral circulation and oxygenation restored
  - Cerebral oxidative metabolism normalized
  - Depressed EEG
  - Decreased cerebral blood flow

## HIE: Secondary Energy Failure



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

## HIE Injury Cascade



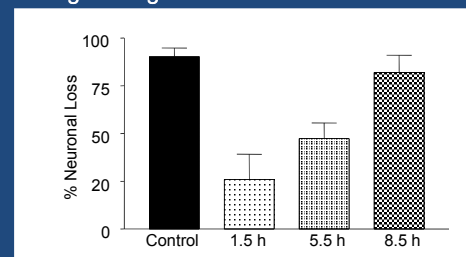
Lai (2010) J Biomed and Biotech

## 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

## Therapeutic Hypothermia

- Outcomes up to 18 months

Study	Hypothermia		Normothermia		Therapeutic Hypothermia	
	Total	Events	Total	Events	Relative Risk	95% CI
CoolCap	198	28	142	26	1.65	0.82 - 3.02
NOH40	102	32	106	22	1.81	0.94 - 3.45
TOBY	163	71	162	45	1.87	1.16 - 3.02
Combined	263	122	210	87	1.75	1.22 - 2.52

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 ®**

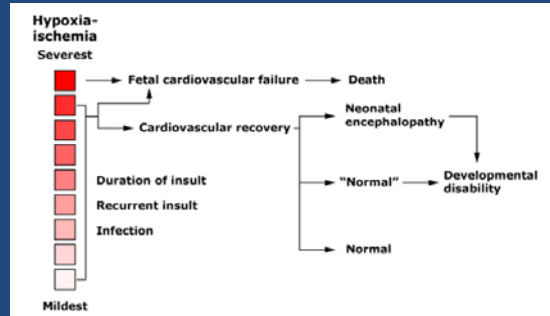
**Toll Free: 1-800-ACH-HELP  
(1-800-224-4357)  
Direct Line: (501) 364-6429**

## 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

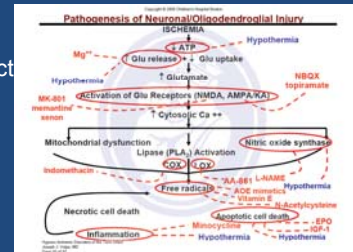
- >40% of infants who receive therapeutic hypothermia still have abnormal outcomes

Outcome	Hypothermia		Normothermia		Relative risk	95% CI start	95% CI end	P value
	Total	Events	Total	Events				
Death or disability	620	123	296	222	0.86	0.71	0.93	0.002
Death	100	10	600	217	0.78	0.66	0.93	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	257	68	227	82	0.73	0.56	0.95	0.01
Blindness	286	20	241	32	0.56	0.33	0.96	0.03

Main neurological outcomes to 18 months of age. For all outcomes studies are Cochrane (20) NICE (21) TOBY (22). For case of death additional studies included are: Akino (13), Shinkawa 2002 (16), Ecker (15), Liu (14), Robinson (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