



# Therapeutic hypothermia for neonatal hypoxic-ischemic encephalopathy



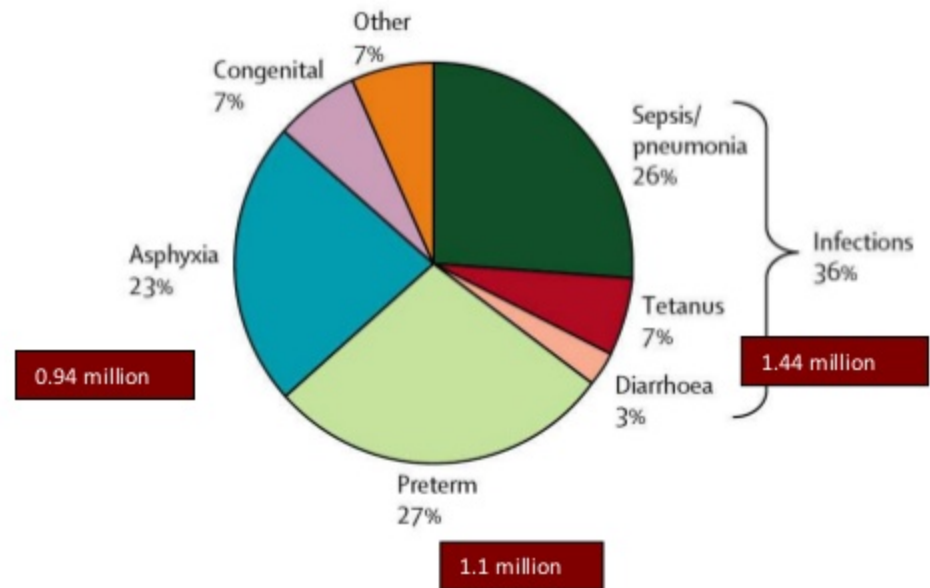
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# HIE in the world

- Major public health issue
- 23% of the total 4 M deaths in the world
- 20% of global incidence of cerebral palsy



# Etiologies of HIE

## ■ Maternal

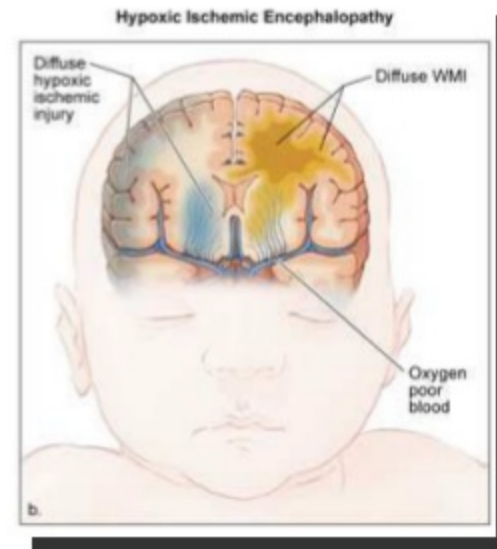
- ☐ Cardiac arrest
- ☐ Asphyxiation
- ☐ Severe anaphylaxis
- ☐ Status epilepticus
- ☐ Hypovolemic shock

## ■ Uteroplacental

- ☐ Placental abruption
- ☐ Cord prolapse
- ☐ Uterine rupture
- ☐ Hyperstimulation with oxytocic agents

## ■ Fetal

- ☐ Fetomaternal haemorrhage
- ☐ Twin to twin transfusion
- ☐ Severe iso-immune haemolytic disease
- ☐ Cardiac arrhythmia





# HIE severity and morbidity/mortality

## Moderately severe

- 1-3 / 1000 livebirths
- Severe handicaps: **30-50%** (epilepsy, cognitive impairment, CP...)
- Mild handicaps: 10-20%
- Normal outcome at 2y: **30-40%**

## Severe

- 0.5-2 / 1000 livebirths
- **Neonatal mortality: 50-75%**
- Severe handicaps: **80%**
- Mild handicaps: 10-20%
- Normal outcome at 2y: **10%**

# Sarnat & Sarnat staging (1976)

	Stage 1	Stage 2	Stage 3
<b>Consciousness</b>	hyperalert	Lethargic or obtunded	Stupor or coma
<b>Activity</b>	Normal	Decreased	Absent
<b>Neuromuscular control</b> Muscle tone Posture Stretch reflexes	Normal Mild distal flexion Overactive	Mild hypotonia Strong distal flexion Overactive	Flaccid Intermittent decerebration Decreased or absent
<b>Primitive reflexes</b> Suck Moro Tonic neck	Weak Strong Slight	Weak or absent Weak, incomplete Strong	Absent Absent Absent
<b>Autonomic function</b> Pupils Heart rate	Normal Tachycardia	Miosis Bradycardia	Mydriasis or variable, unequal Variable
<b>Seizures</b>	None	Common	Uncommon

Stage 0 = Normal



# Early evaluation of HIE

- Early and repeated clinical examination: **Classification de Sarnat et Sarnat staging+++**
- Clinical investigations:
  - **EEG**: early, continuous recording using either standart EEG or aEEG
  - **Ultra sonographic scan**: easy and early but non specific  
*as early as possible*

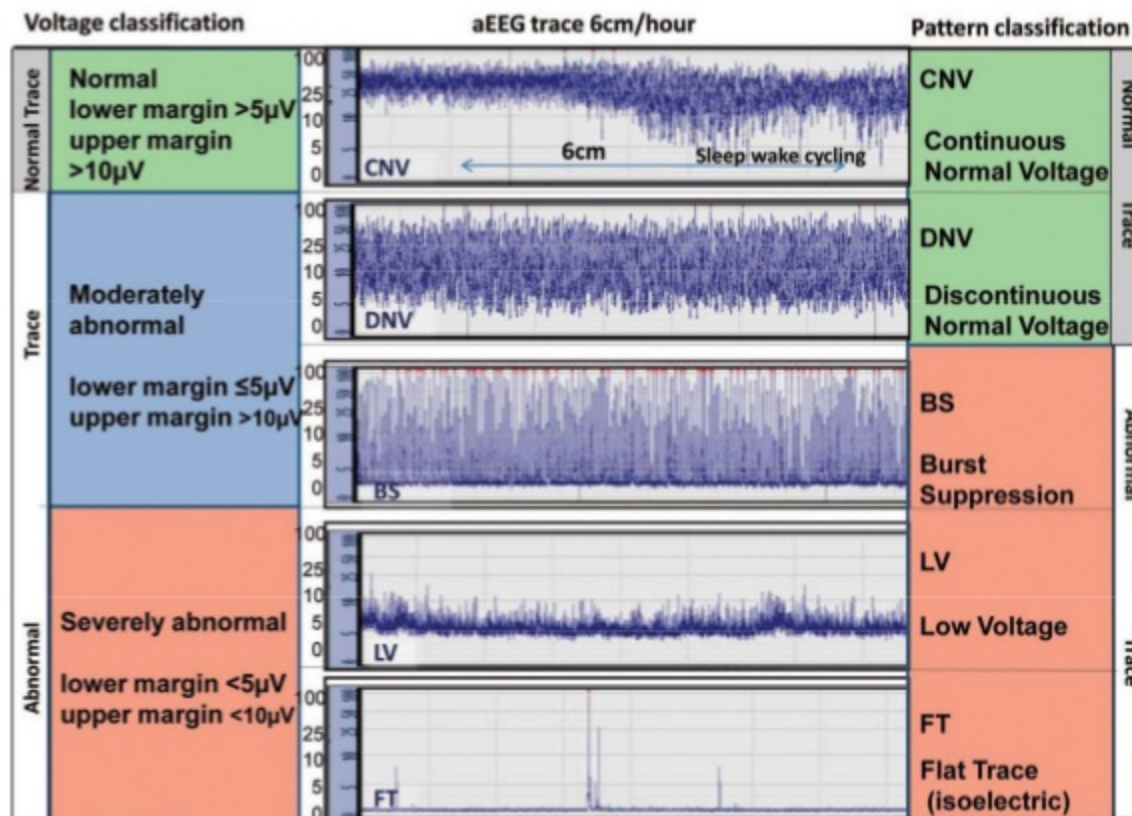
➡ Short term prognosis. Therapeutic management: **HYPOTHERMIA?**

- **MRI: standard sequences + Diffusion +/- DTI + MRSpectroscopy:**  
*between day 3 and day 8 +/- day 10-15*

➡ Long term outcome.

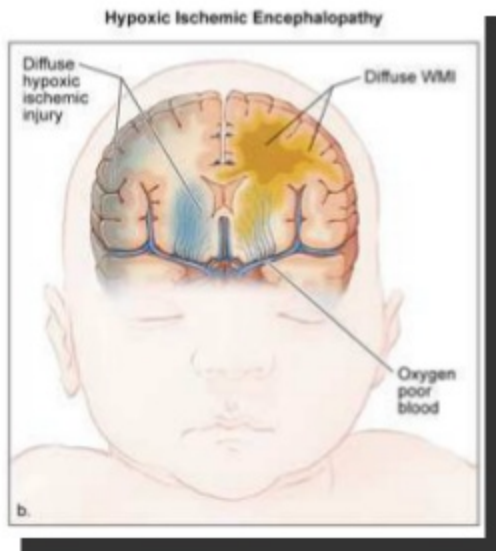


# Amplitude EEG features in HIE



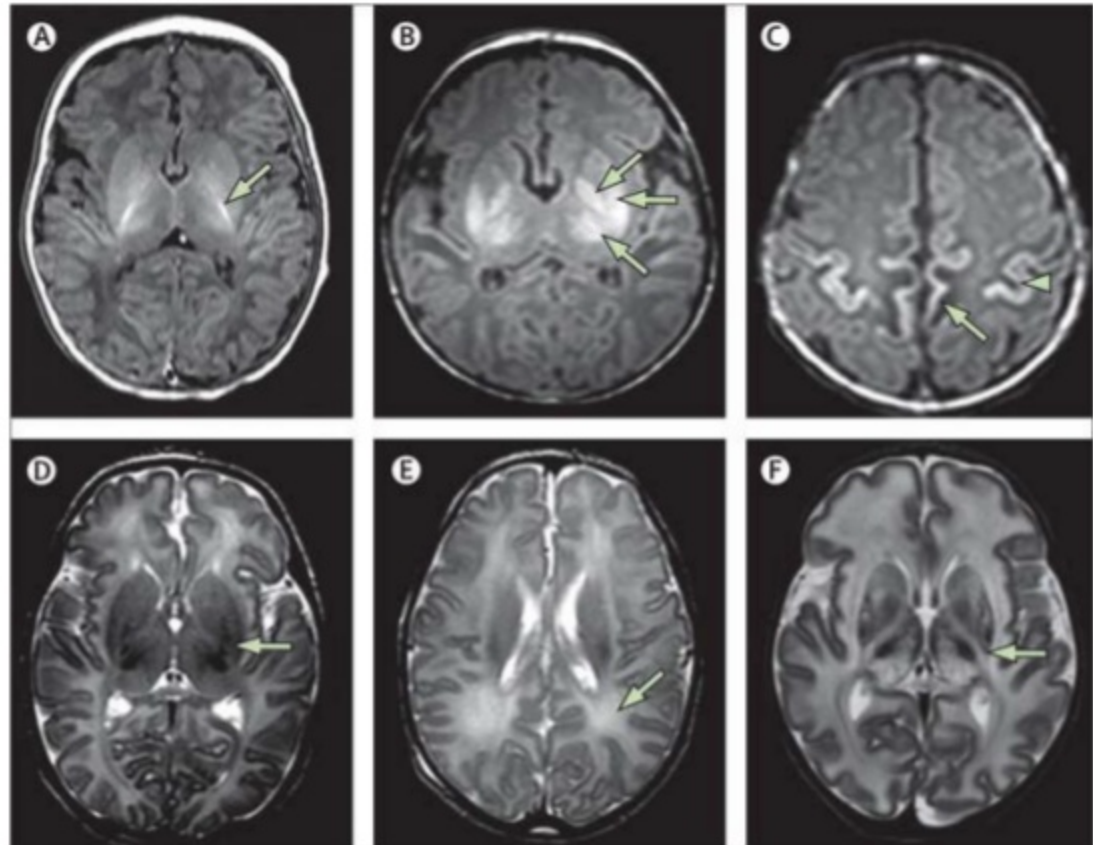
From Thoresen M, et al. Effect of hypothermia on amplitude-integrated electroencephalogram in infants with asphyxia. Pediatrics. 2010 Jul;126(1):e131-9. PMID:9563847 Reprinted with permission of The American Academy of Pediatrics

# HIE and MRI features



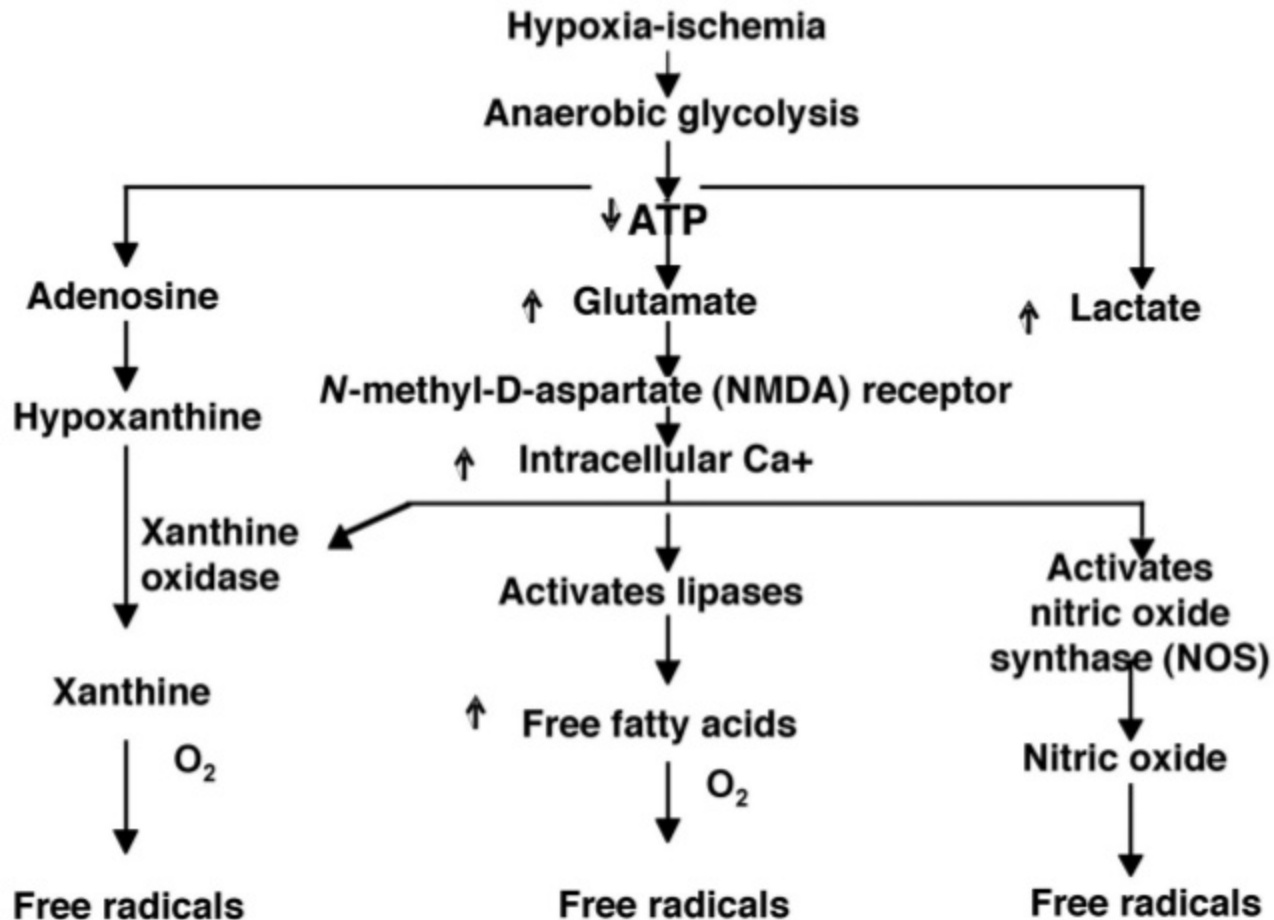
- Basal ganglia and thalami
- Cortical enlighting
- Post limb of internal capsule
- White matter

**normal**

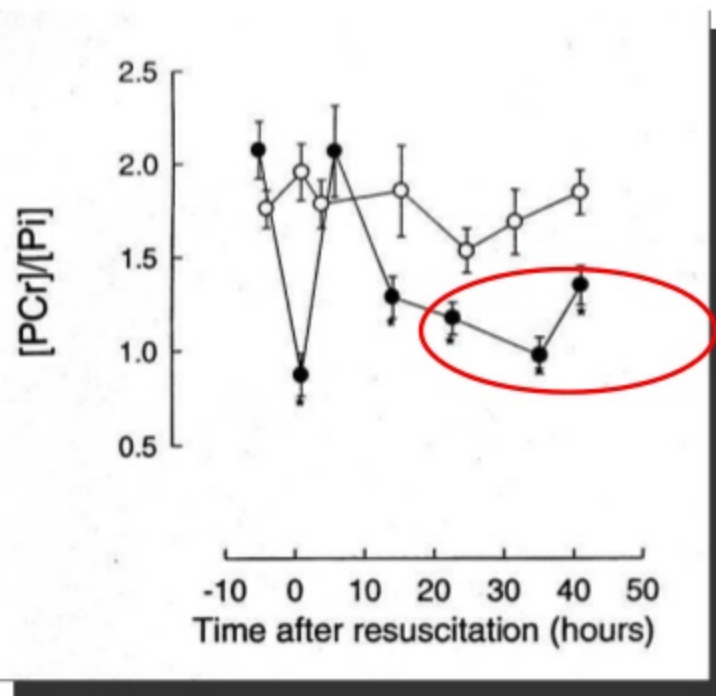




# Potential pathways for HIE-induced injury



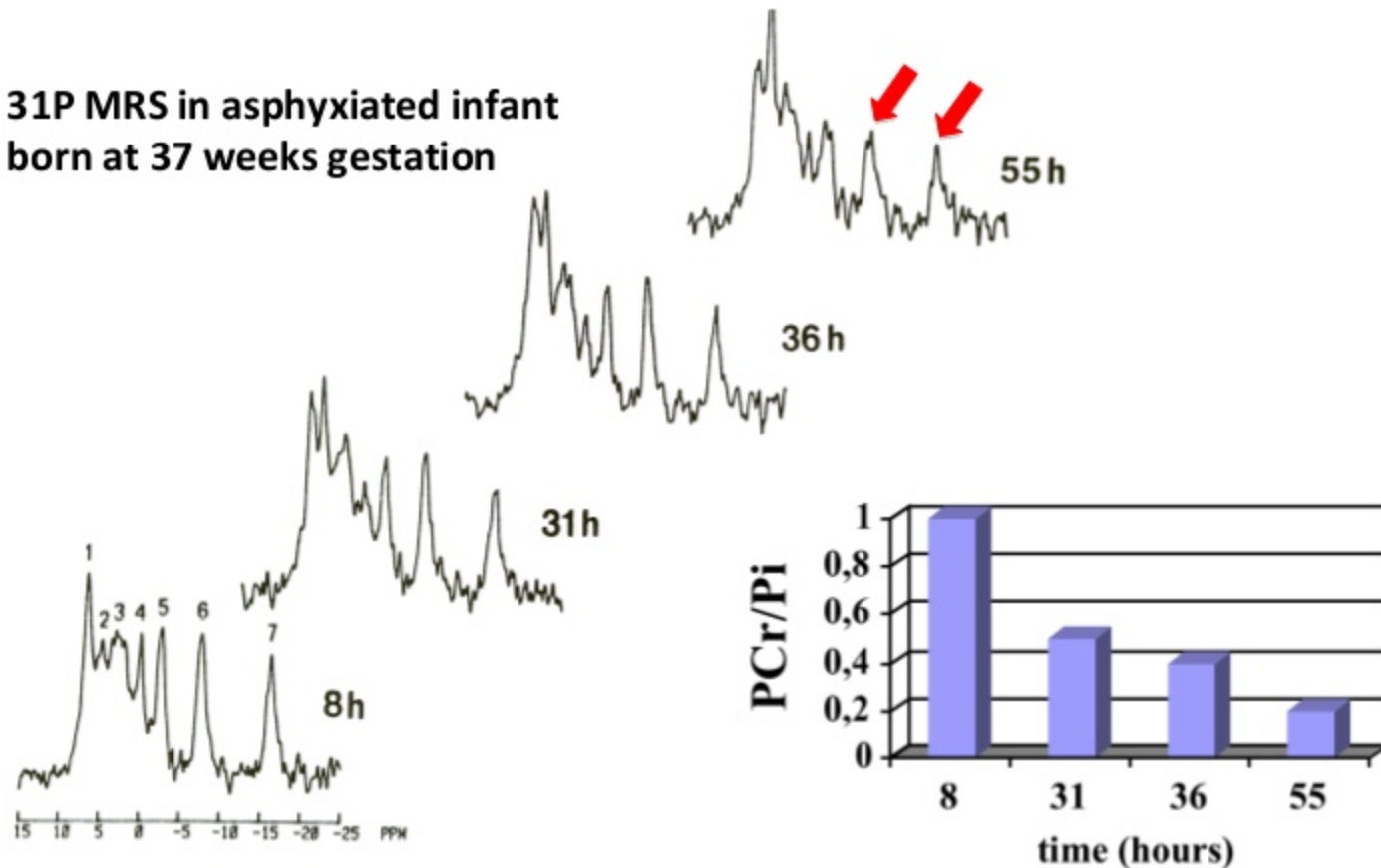
# HIE and energy failures



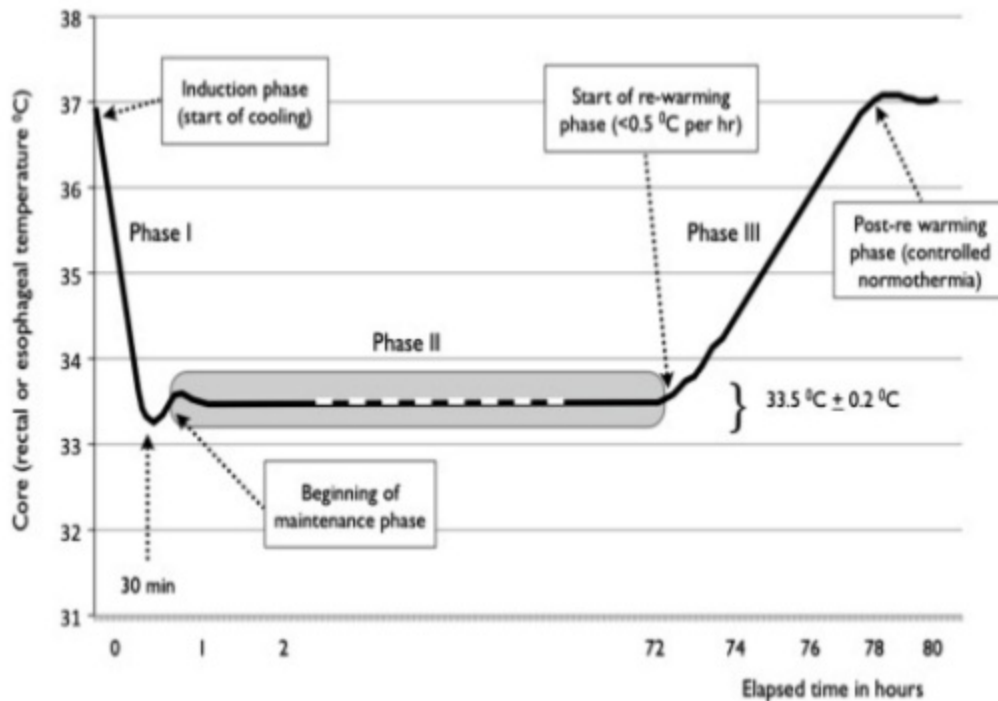
- First energy failure during HIE
- Rapid recovery
- Secondary energy failure after 6-12h post HIE
- Mitochondrial insult
- Cell death and apoptosis

# Brain metabolism is normal following resuscitation but deteriorates later

**$^{31}\text{P}$  MRS in asphyxiated infant  
born at 37 weeks gestation**



# Hypothermia: concept

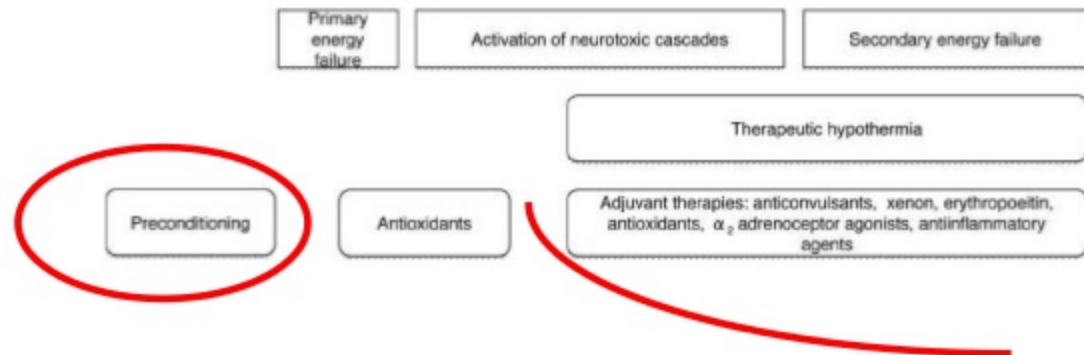
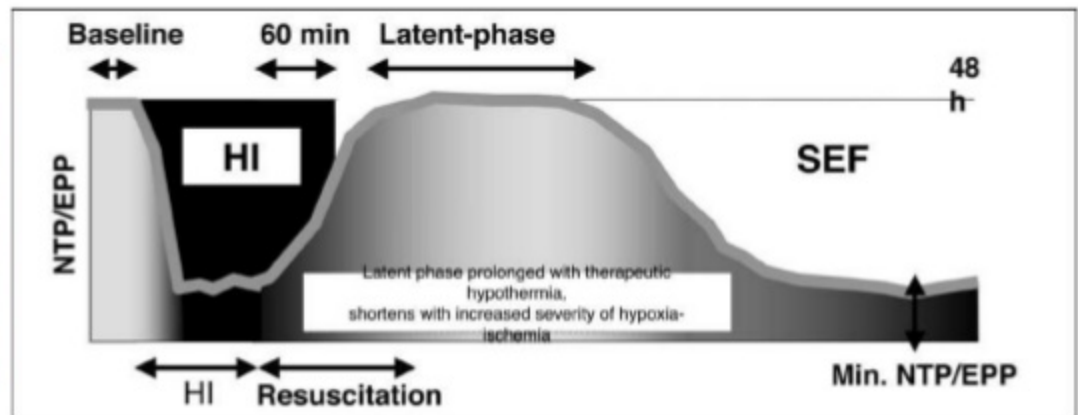
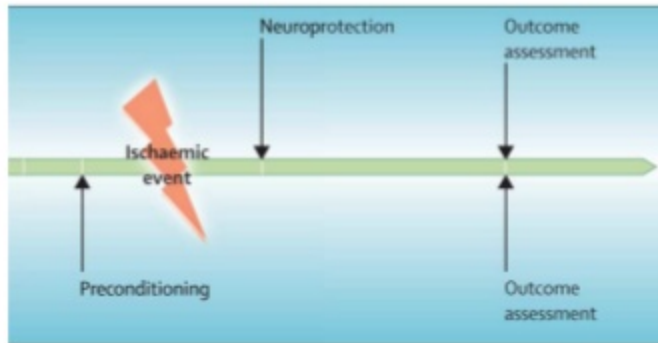


- To induce a stable central temperature around  $33.5^{\circ}\text{C} \pm 0.5^{\circ}\text{C}$
- Before 6 hours of life
- In the most stable manner
- For a 72h duration
- Progressive and cautious rewarming  $0.2^{\circ}\text{C} / \text{h}$

# Hypothermia:

## A post-conditioning concept

### Post-Cond





## Hypothermia: cellular effects

- Reduces cerebral metabolism, prevents edema
- Decreases energy utilization
- Reduces/suppresses cytotoxic amino acid accumulation (glutamate) and nitric oxide
- Inhibits platelet-activating factor, inflammatory cascade
- Attenuates secondary neuronal damage and cell death
- Reduces extent of brain damage
- Prevention of blood brain barrier disruption





## Experimental evidence supporting therapeutic hypothermia

- Hypothermia applied *after* HIE:
  - Reduces elevation of dopamine, free fatty acid and glutamate
    - Stroke 1989 ;20:904-10.
  - Preserves cerebral energy metabolism
    - Pediatr Res 1995 ;37:667-670; Pediatr Res 1997 ;41:803-808
  - Reduces the delayed increase in extracellular glutamate
    - Neuroreport 1997 ;8:3359-62
  - Reduces the secondary rise in cortical impedance (cytotoxic oedema)
    - Pediatrics 1998 ;102:1098-1106
  - Inhibits apoptotic cell death
    - Neuropathol Appl Neurobiol 1997 ;23:16-25

# Hypothermia

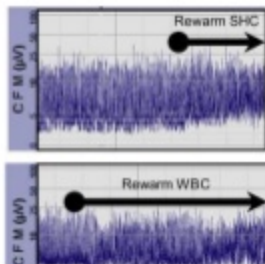
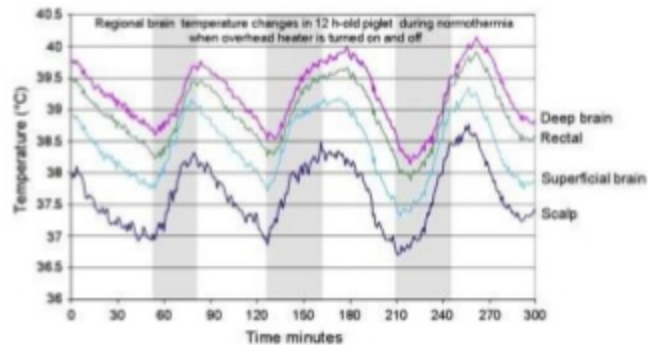


**Head cooling  
or  
total body cooling**

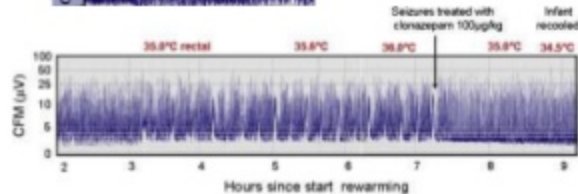


# Hypothermia: monitoring is crucial

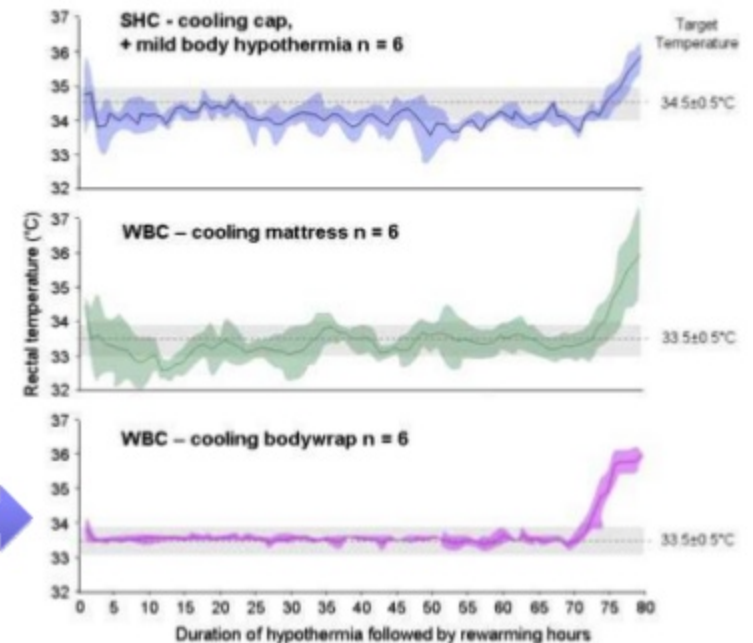
## Brain regional temperatures in piglet



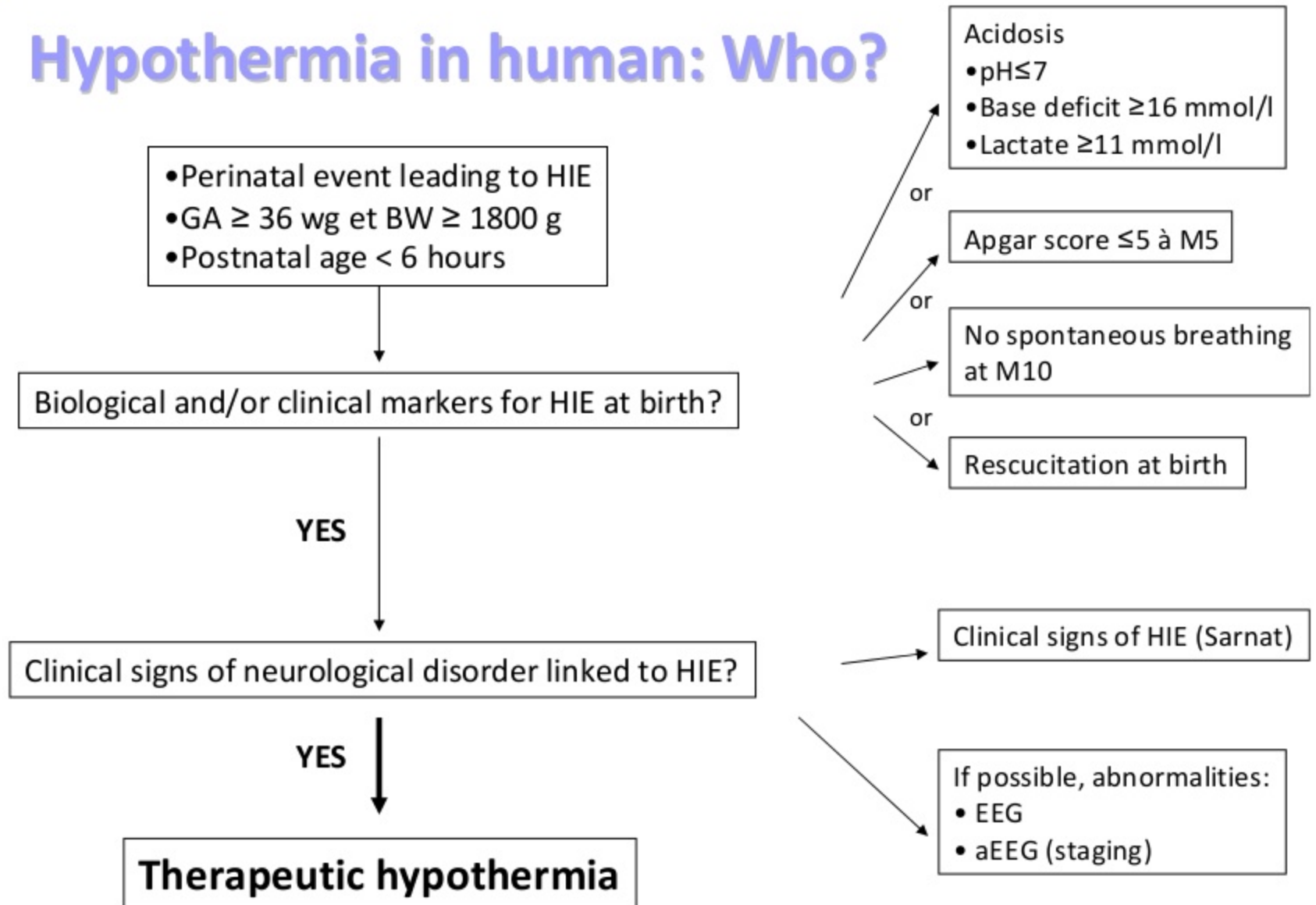
## Seizures during rewarming



## Temperature stability according to devices



# Hypothermia in human: Who?



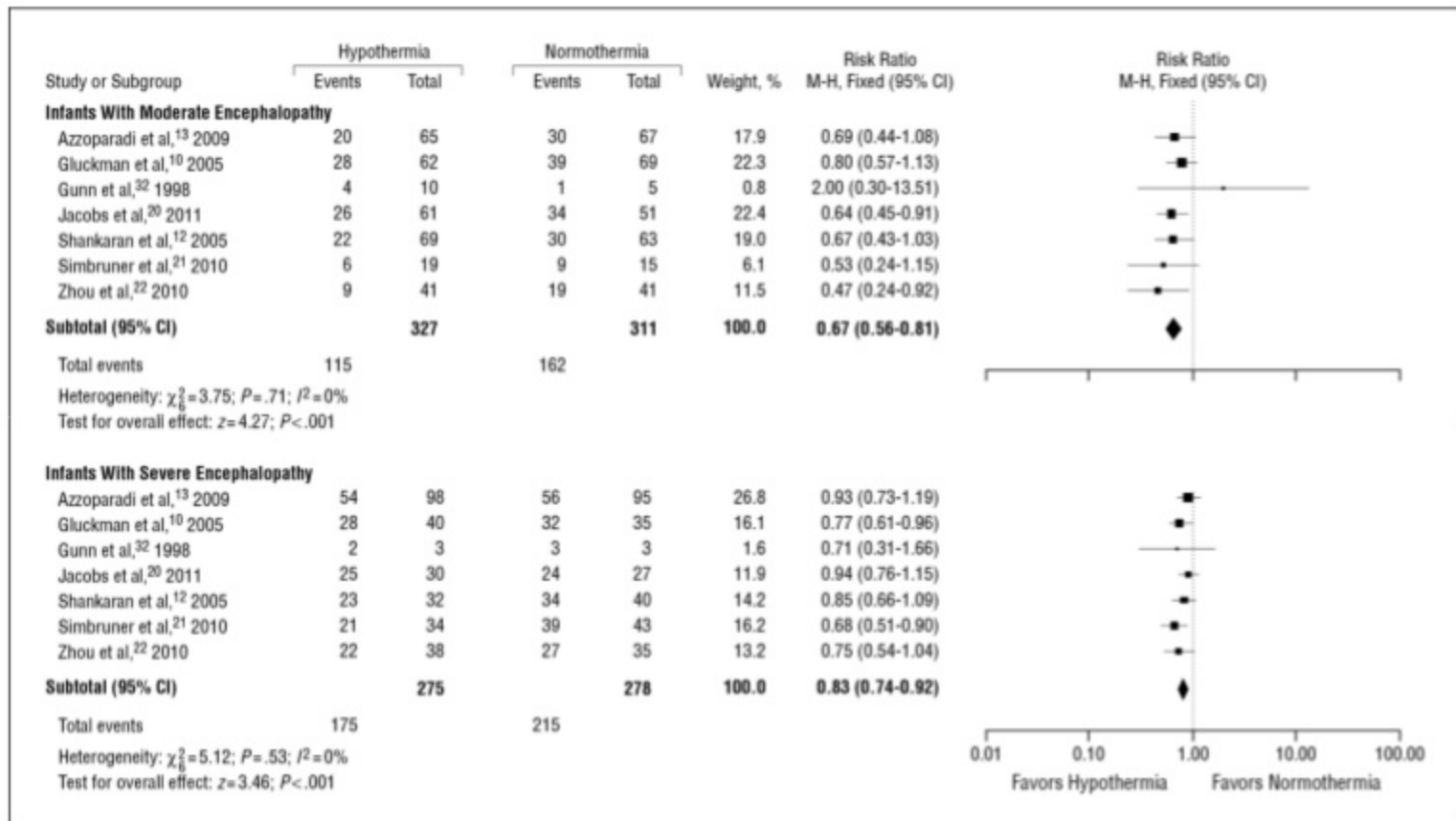


## Hypothermia and biological markers

- Heart rate: ↘ 14 bpm/min
- PaCO<sub>2</sub>: ↘ 2 mmHg
- pH: ↗ 0,12 unité
- Leak of NaCl, KCl and Mg<sup>2+</sup>
- ↗ blood viscosity
- ↘ Platelets
- ↗ Insulin resistance
- ↘ WBC
- ↗ Pharmacokinetics of morphine and anti-epileptic drugs



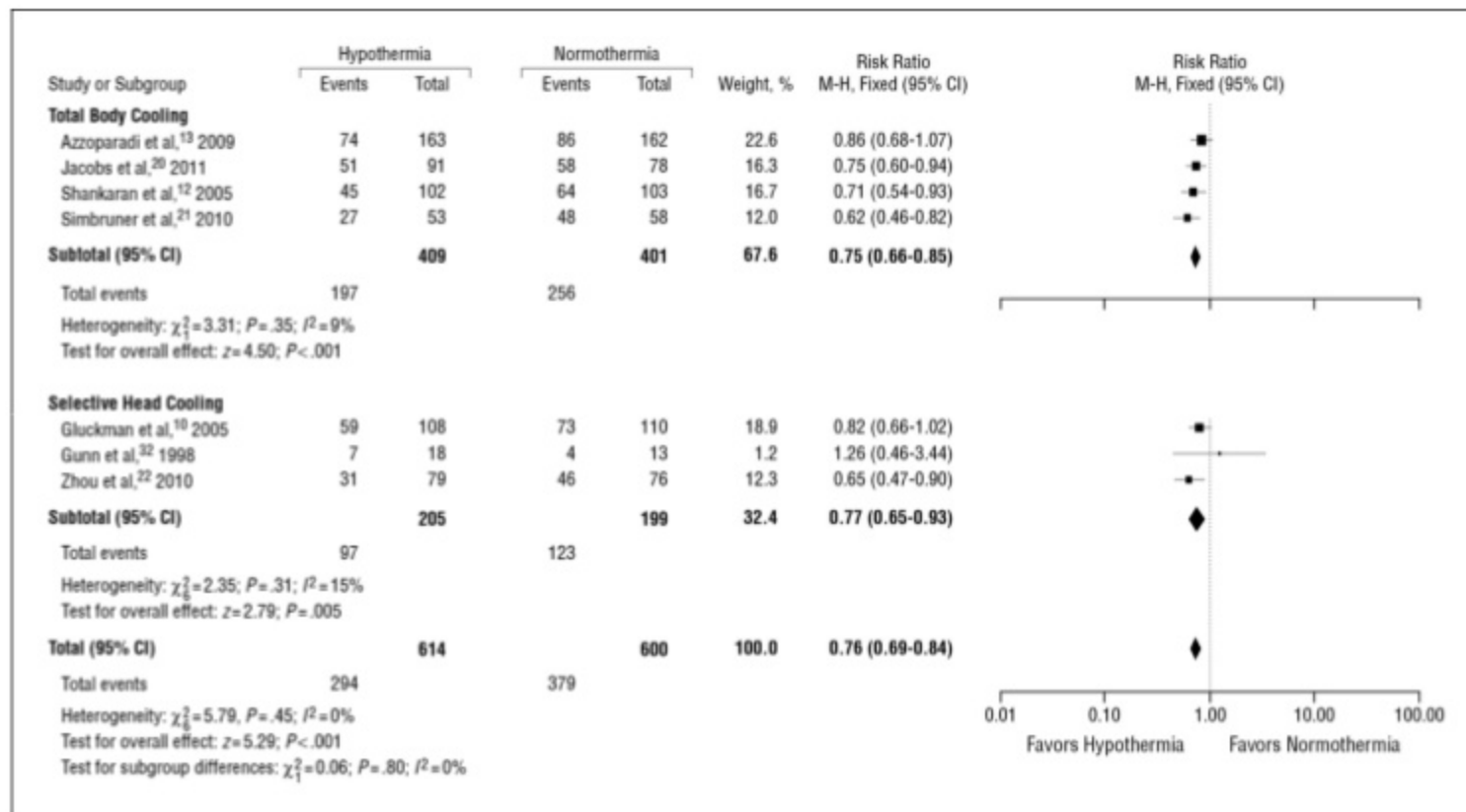
# Beneficial effect of hypothermie according to HIE severity



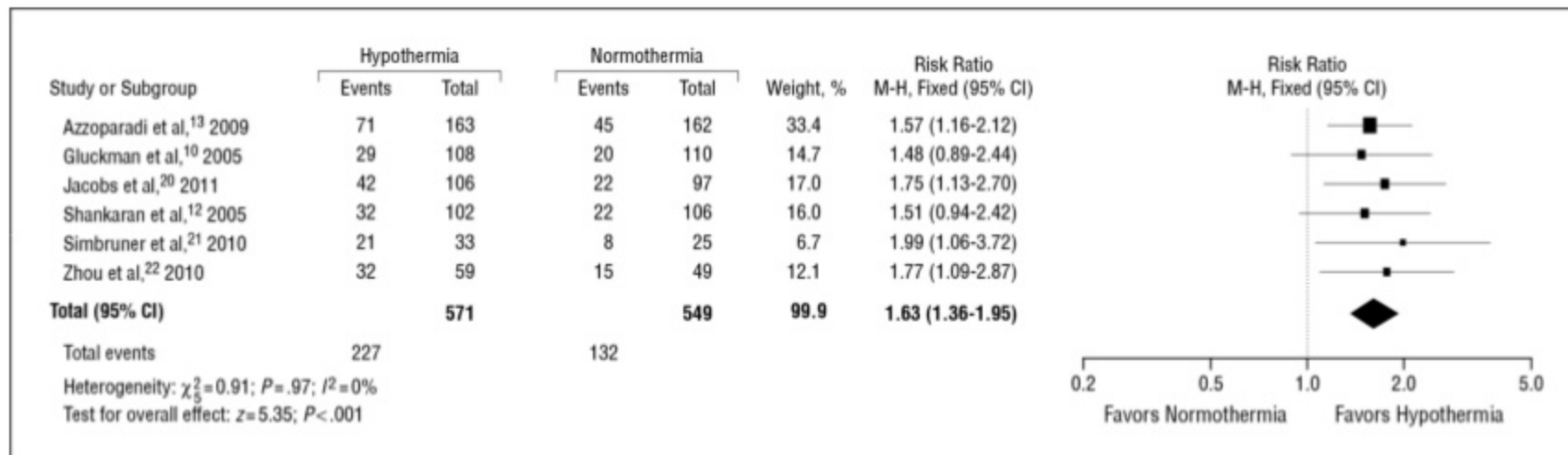
NNT 6-8



# Beneficial effect of hypothermie according to cooling technique



# Normal outcome following hypothermia for HIE



# Impact of hypothermia on MRI findings

	Cooled (n=64)	Non-cooled (n=67)	Adjusted*		Unadjusted*	
			OR (95% CI)	p	OR (95% CI)	p
Basal ganglia and thalami						
0	26	14	0.36 (0.15-0.84)	0.02	0.39 (0.18-0.84)	0.02
1	11	14				
2	11	14				
3	16	25				
Posterior limb of internal capsule						
Normal	34	23	0.38 (0.17-0.85)	0.02	0.46 (0.23-0.93)	0.03
Equivocal	2	5				
Abnormal	28	39				
White matter						
Normal	23	11	0.30 (0.12-0.77)	0.01	0.35 (0.15-0.80)	0.01
1	19	26				
2	15	21				
3	7	9				
Cortex†						
0	34	24	0.62 (0.27-1.41)	0.25	0.65 (0.29-1.42)	0.28
1	16	22				
2	10	16				
3	4	4				
Intracranial haemorrhage	25	22	Not done		1.31 (0.64-2.68)	0.11

Data are number or OR (95% CI). \*Odds ratio for presence or absence of MRI abnormalities in cooled and non-cooled infants, with and without adjustment for severity of amplitude integrated EEG and postnatal age. OR=odds ratio. †Cortex could not be assessed in one infant in the non-cooled group.

**Table 2: Grades of cerebral lesions seen on MRI in cooled and non-cooled infants**

Therapeutic hypothermia reduces basal ganglia and WM lesions...  
... but has no effect on cortical damage

	Cooled* (n=63)	Non-cooled (n=67)	Total
<8 days			
MRI abnormalities absent			
Not disabled	10	11	21
Died or disabled	0	1	1
Total	10	12	22
MRI abnormalities present			
Not disabled	1	7	8
Died or disabled	16	13	29
Total	17	20	37
≥8 days			
MRI abnormalities absent			
Not disabled	21	12	33
Died or disabled	3	1	4
Total	24	13	37
MRI abnormalities present			
Not disabled	6	4	10
Died or disabled	6	18	24
Total	12	22	34

	Cooled	Non-cooled
Sensitivity	0.88 (0.79-0.97)	0.94 (0.88-1.0)
Specificity	0.82 (0.72-0.92)	0.68 (0.56-0.80)
Positive predictive value	0.76 (0.65-0.87)	0.74 (0.63-0.85)
Negative predictive value	0.91 (0.83-0.99)	0.92 (0.85-0.99)

Therapeutic hypothermia makes MRI abnormalities more specific to poor outcome



## Mid- long-term outcomes: neurocognitive/behavior scales

### ☐ **12-30 months: Bayley**

- (Eicher & al., 2004; Jacobs & al., 2011; Shankaran & al., 2005)

### ☐ **6-7 years: WPPSI-III / WISC-IV / NEPSY / M-ABC**

- (Marlow & al., 2005; Shankaran & al., 2012)

### ☐ **9-10 years: WISC-III / M-ABC / CBCL**

- (de Verries & Jongmans, 2010)



# Childhood outcomes after hypothermia for HIE

## ■ Objective

- ☐ Long term evaluation (6-7 y) of infants having experienced hypothermia for HIE

## ■ Methods and patients

- ☐ 208 infants with HIE 2-3 at birth
- ☐ 93 controls (6 y 8 m) vs 97 hypothermia( 6 y 7 m)
- ☐ 18 lost (15% of surviving)
- ☐ Motor : GMFCS / Intellect : WPPSI-III & WISC-IV / Attention, FE, Visuo-spatial : NEPSY / Emotional & Social : Child Health Questionnaire

# Childhood outcomes after hypothermia for HIE

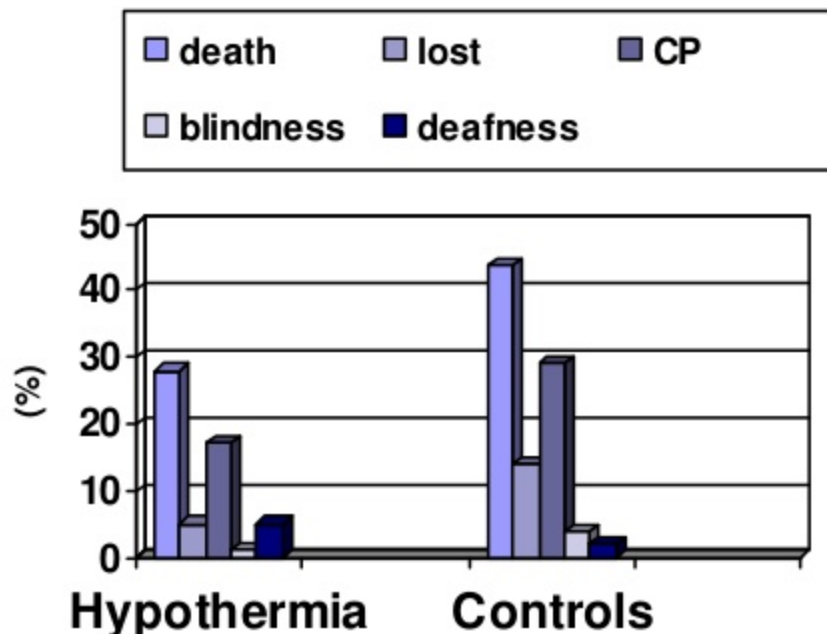
## ■ Results

### □ Hypothermia ( n = 97)

- 27 deaths (28 %)
- 5 lost (5 %)
- 12/69 CP (17 %)
- 1/67 blindness (1 %)
- 3/63 deafness (5%)

### □ Controls (n = 93)

- 41 deaths (44 %)
- 13 lost (14 %)
- 15/52 CP (29 %)
- 2/50 blindness (4 %)
- 1/50 deafness (2%)







# Childhood outcomes after hypothermia for HIE

## ■ Results

### □ Hypothermia

- 19/70 IQ < 70 (27 %)
- 2/48 dysexecutive functions (< 70) (4 %)
- 2/53 visuo-spatial impairment (< 70) (4 %)

### □ Controls

- 17/52 IQ < 70 (33 %)
- 4/32 dysexecutive functions (< 70) (13 %)
- 1/36 visuo-spatial impairment (< 70) (3 %)

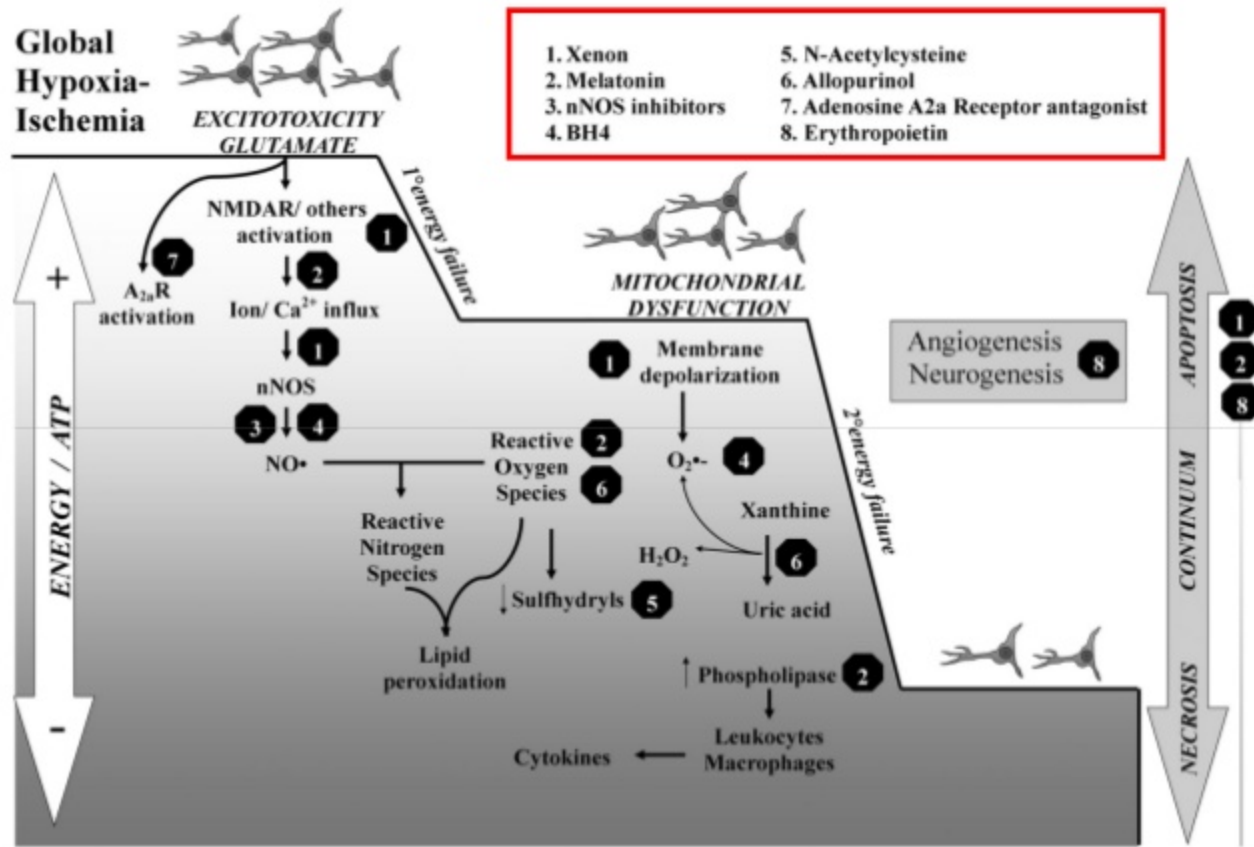


# Childhood outcomes after hypothermia for HIE

## ■ Interpretation

- ☐ No significant difference:
  - CP
  - IQ at 6-7 y
  - Emotional skills
- ☐ 15% lost of follow up
- ☐ Behavior and school performances?
- ☐ Appropriate scales?

# Hypothermia + neuroprotective agents



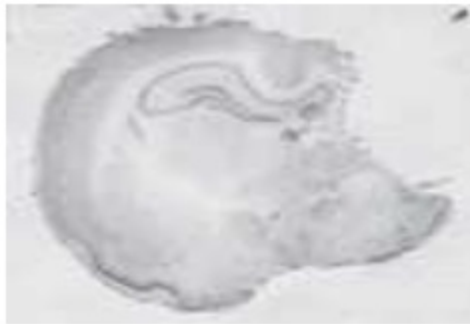
# Promising candidate molecules to be associated with hypothermia

	Melatonine	Epo	NAC	Epo mimetics	Allopurinol	Xenon	Vit C&E	Memantine	Topiramate	Adenosine A2A rec antag
Easy to use	10	10	10	10	7	4	9	3	4	5
Regimen	7	7	7	7	8	6	6	5	4	5
SAE	10	8	10	8	8	8	6	6	5	8
Toxicity	10	10	10	7	10	8	8	10	9	2
Benefits	8	8	3	6	3	8	4	3	3	5
FDA approval	yes	yes	yes	no	yes	no	yes	yes	yes	no
Total score /50	45	43	40	38	36	34	33	27	25	22
Rank % score	1 (90%)	2 (86%)	3 (80%)	4 (76%)	5 (72%)	6 (68%)	7 (66%)	8 (54%)	9 (50%)	10 (44%)

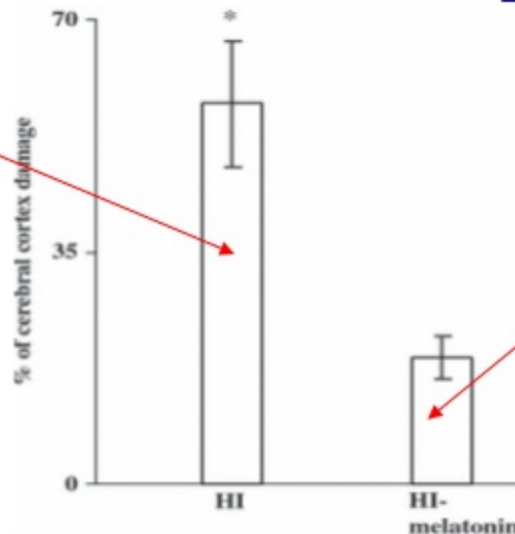


# Hypothermia and melatonin

- Anti-oxidant, anti-excitotoxic and anti-inflammatory agent
- High innocuity

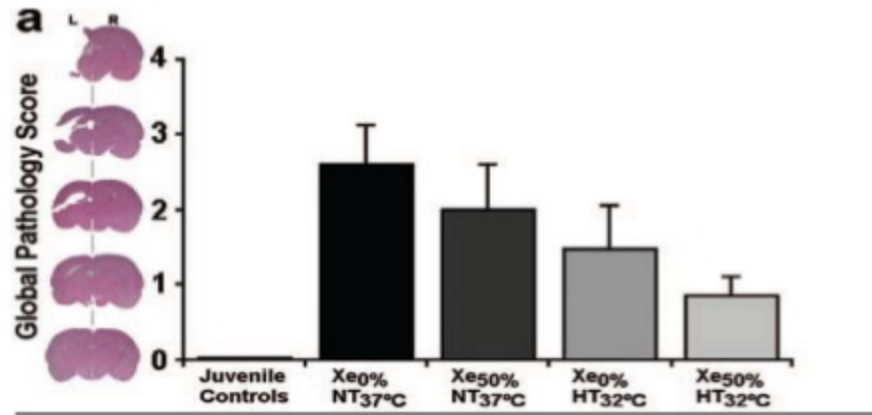


- Melatonin in neonatal rat models of HIE
  - Reduced lesion score ( $p < 0,05$ )
  - Reduced ROS accumulation ( $p < 0,05$ )
  - Better behavioral scores ( $p < 0,05$ )



Fulia F et al, *J Pineal Res* 2001; 31(4):343-9  
Signorini C et al, *J Pineal Res* 2009; 46(2):148-54  
Carlioni S et al, *J Pineal Res* 2008; 44(2):157-64  
Gitto E et al, *J Pineal Res* 2009; 46(2):128-39

# Hypothermia and inhaled Xenon



- Synergistic effect of hypothermia in pre-clinical model using hypothermia (32°C) and **inhaled Xenon** (50%) (rats subjected to HIE) :
  - Hypothermia alone was associated with early and long-term behavior improvement ( $p < 0.001$ )
  - Xenon alone was associated with long-term behavior improvement ( $p < 0.05$ )
  - **Both hypothermia and Xenon were associated with better histological scores** ( $p < 0.05$ )



# Deleterious co-factors to be avoided

## ■ Prevention of additional insult :

- ☐ Pain
- ☐ Subclinical seizures
- ☐ Neurosensory dystimulation
  
- ☐ Ionic disorders
  
- ☐ Adequat use of oxygen
- ☐ Rewarming
  
- ☐ Developmental care





## Conclusion

- HIE trigger is poorly understood → public health issue
- More than 1M deaths and 2M infants with neurocognitive impairments / year
- Therapeutic hypothermia is feasible, safe in referral centers and efficient at mid-term if initiated before 6h of life ... but impact in long-term outcomes?
- Hot topics for neuroprotective strategies
  
- ... the future → combination of hypothermia + other pharmacological agent(s)