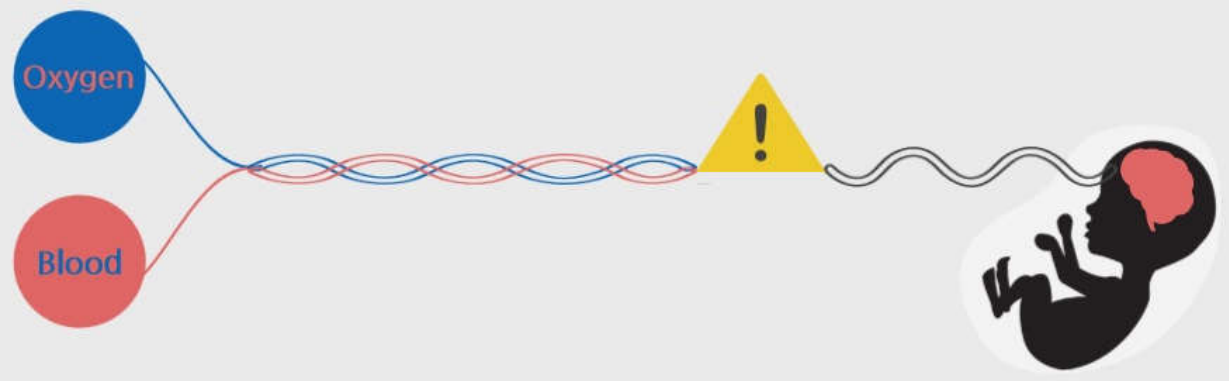
Neonatal Hypoxic – Ischemic Encephalopathy

Treatment Approaches from Evidence



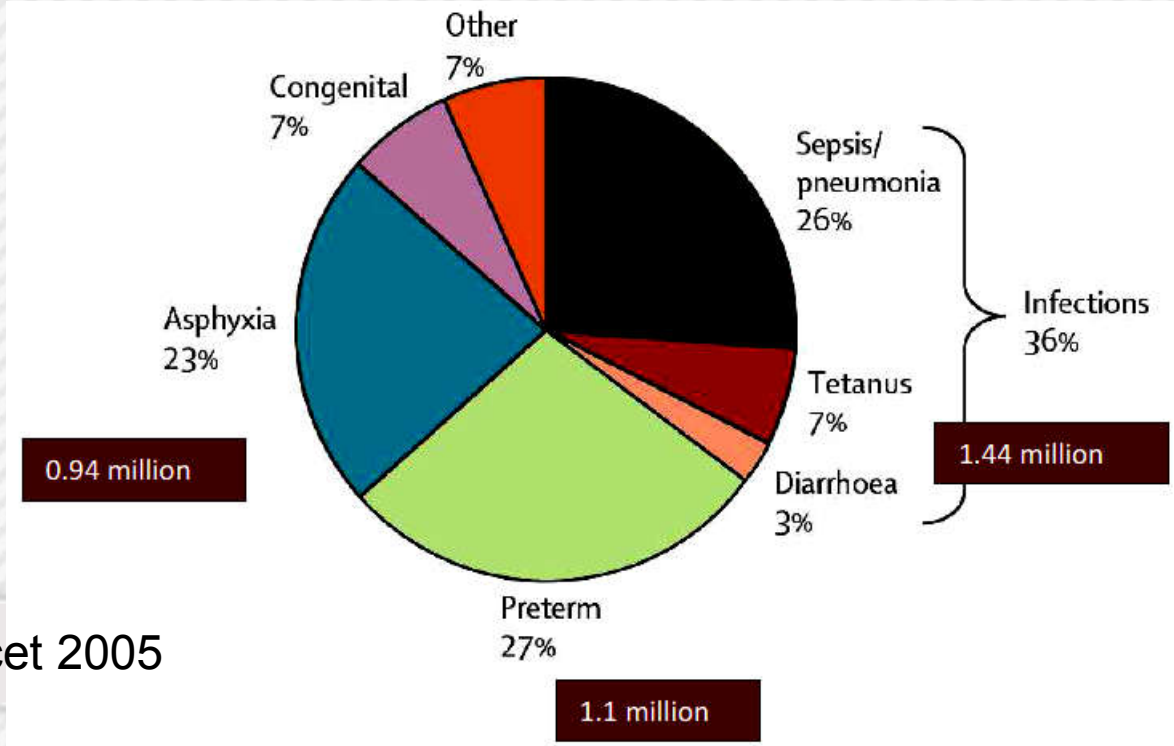
Dr. Nguyen Pham Minh Tri – NICU – Children's Hospital 2

Content

1. Introduction
2. HIE and Hypothermia
3. Other combination treatments
4. Conclusion

HIE in the world

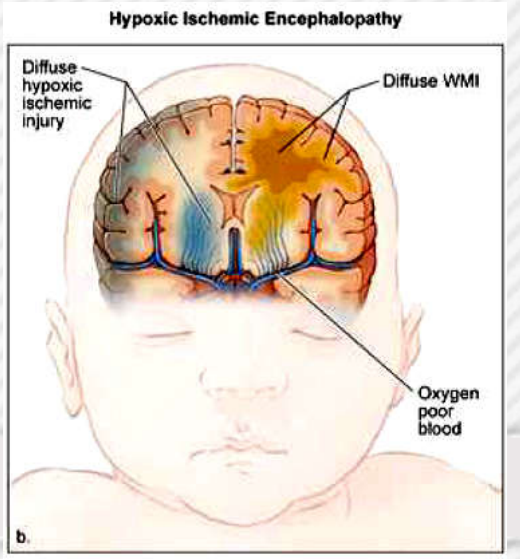
- Major public health issue
- 23% of the total 4 M deaths in the world
- 20% of global incidence of cerebral palsy



Lawn JE et al, Lancet 2005

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	Severe
▪ **1-3 / 1000** livebirths	▪ **0.5-2 / 1000** livebirths
	▪ Neonatal mortality: **50-75%**
▪ Severe handicaps: **30-50%** (epilepsy, cognitive impairment, CP…)	▪ Severe handicaps: **80%**
▪ Mild handicaps: **10-20%**	▪ Mild handicaps: **10-20%**
▪ Normal outcome at 2y: **30-40%**	▪ Normal outcome at 2y: **10%**

Early evaluation of HIE

- Early, **repeated** clinical examination**: Sarnat staging+++**
- Clinical investigations:
  - **EEG**: early, continuous recording / standard EEG or aEEG
  - **Ultrasonography**: easy but non specific, ***as early as possible***

→ **Short term prognosis. HYPOTHERMIA?**

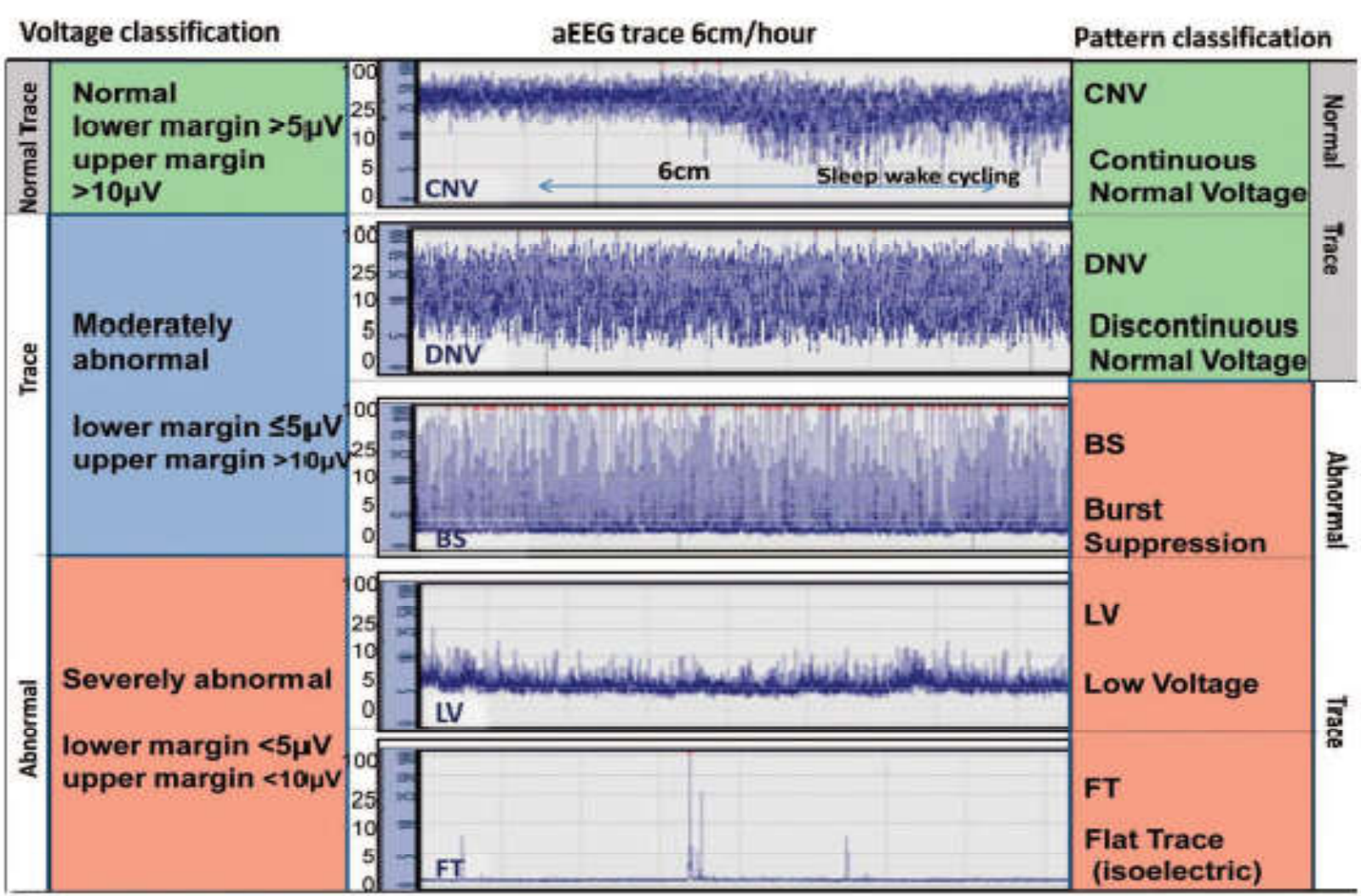
  - **MRI: standard sequences + Diffusion +/- DTI + MRSpectroscopy**: ***btw day 3 - day 8 +/- day 10-15***

→ **Long term outcome**.

Sarnat grading scale for HIE

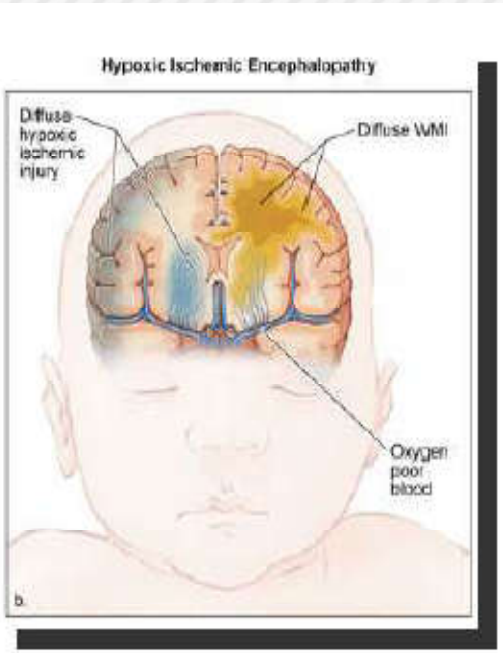
	Grade 1 (mild)	Grade2 (moderate)	Grade 3 (severe)
Level of consciousness	Irritable/hyperalert	Lethargy	Coma
Muscle tone	Normal or hypertonia	Hypotonia	Flaccid
Tendon reflexes	Increased	Increased	Depressed or absent
Seizures	Absent	Frequent	Frequent
Complex reflexes	Normal	weak	Absent
Prognosis	Good (100%) Normal	Variable (80%) Normal	High mortality and neurological disability (50% Death 50% major sequelae)

Amplitude EEG features in HIE

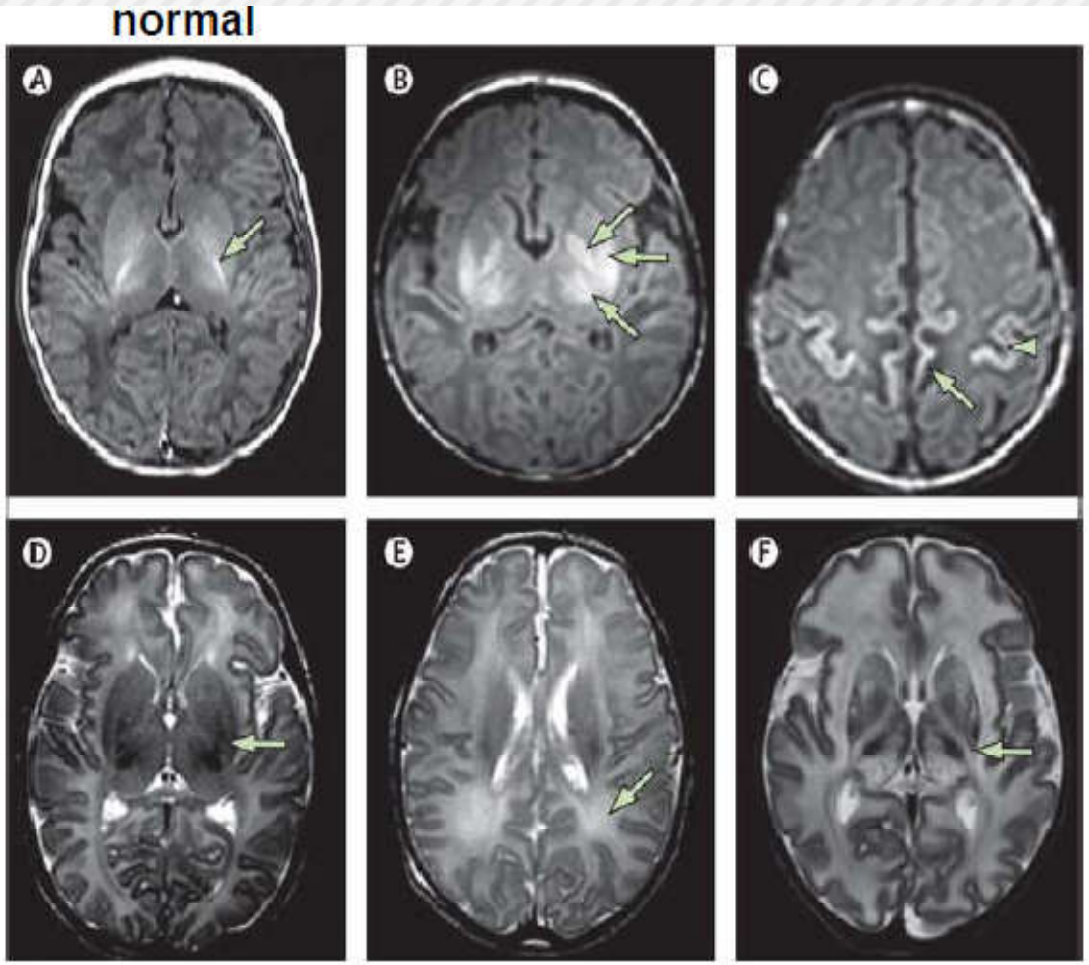


From Thoresen M, et al. Effect of hypothermia on amplitude-integrated electroencephalogram in infants with asphyxia. Pediatrics. 2010 Jul;126(1):e131-9. PMID:9563847 Reprinted with permission of The American Academy of Pediatrics

HIE and MRI features



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



Rutherforf et al., Lancet 2010

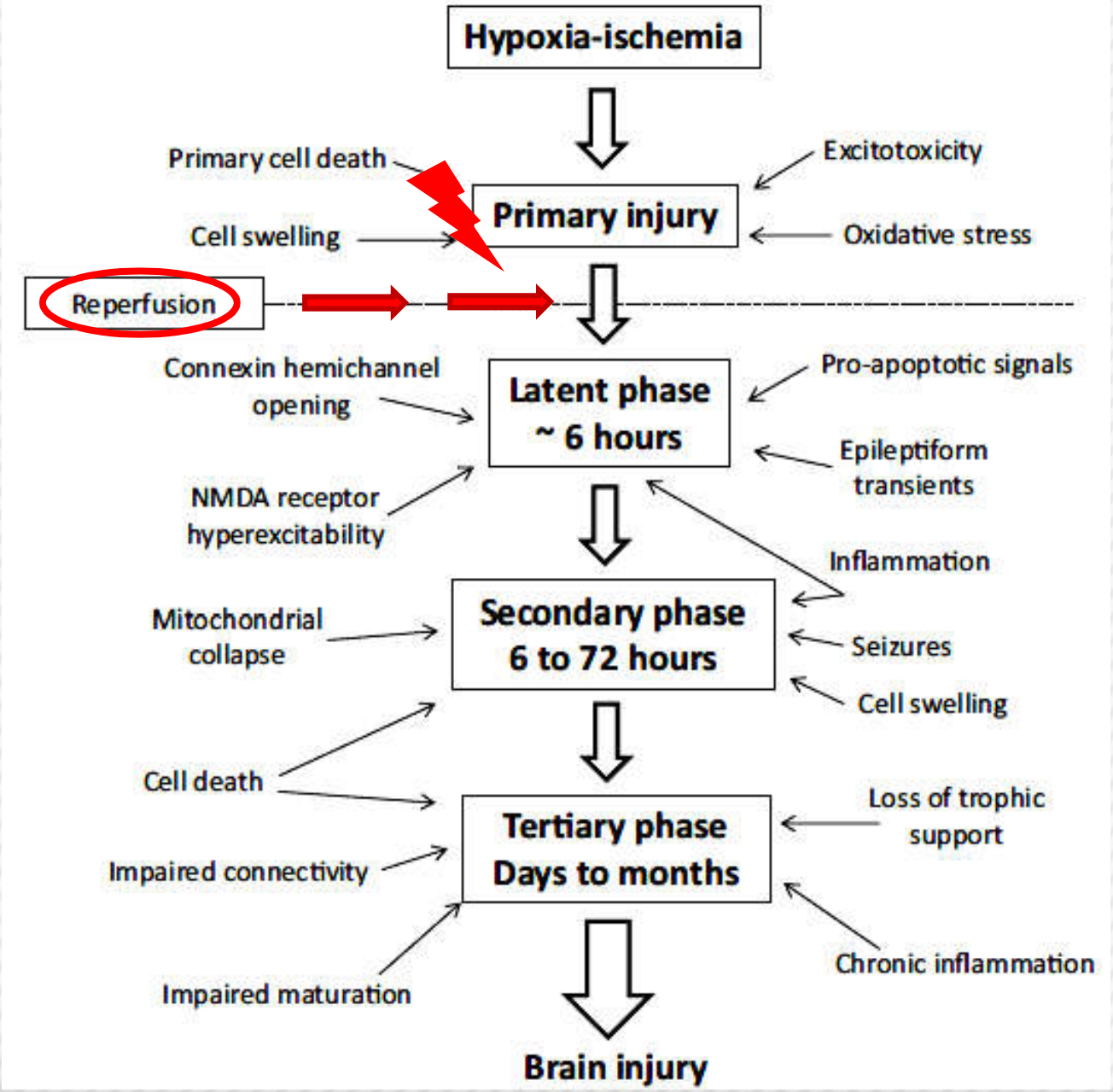
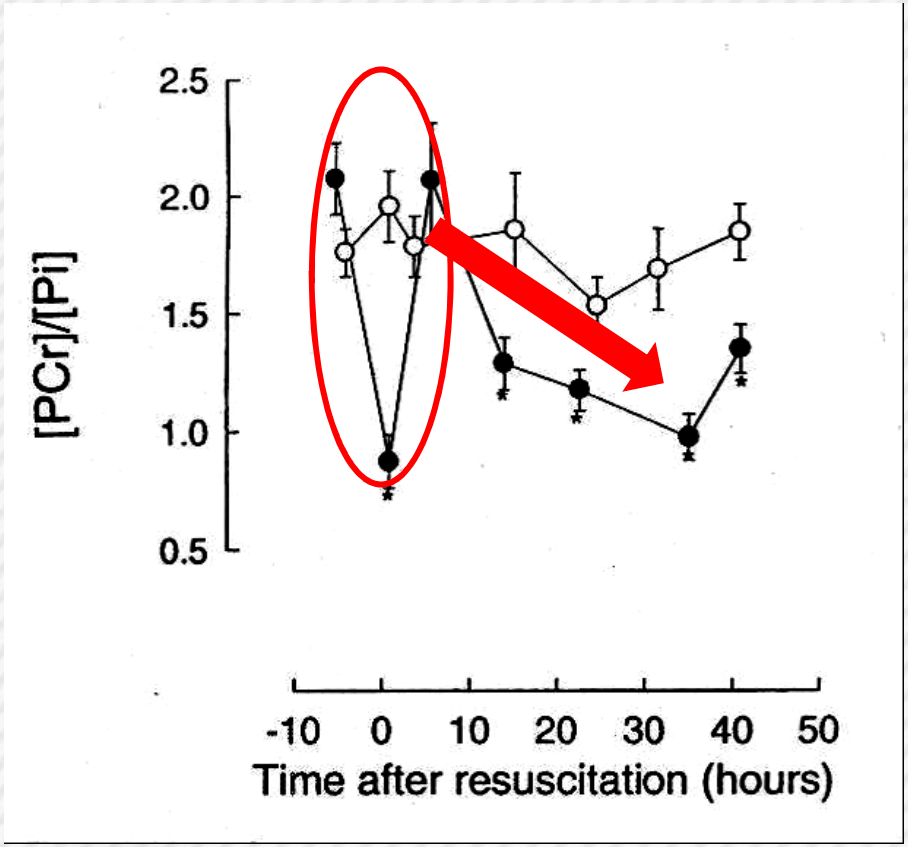


Figure 1: Mechanisms of evolving neural injury in HIE

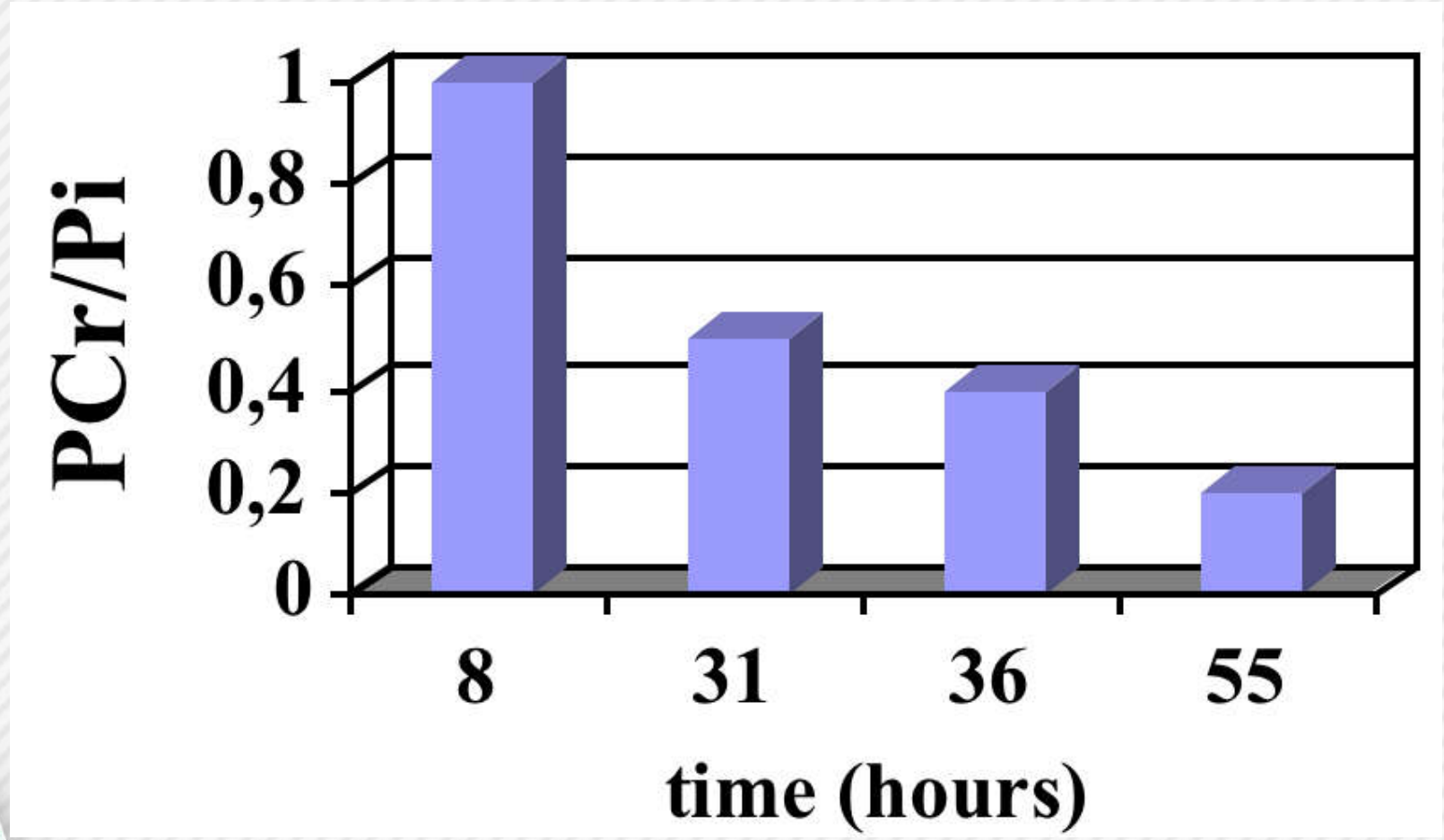
HIE and energy failures



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

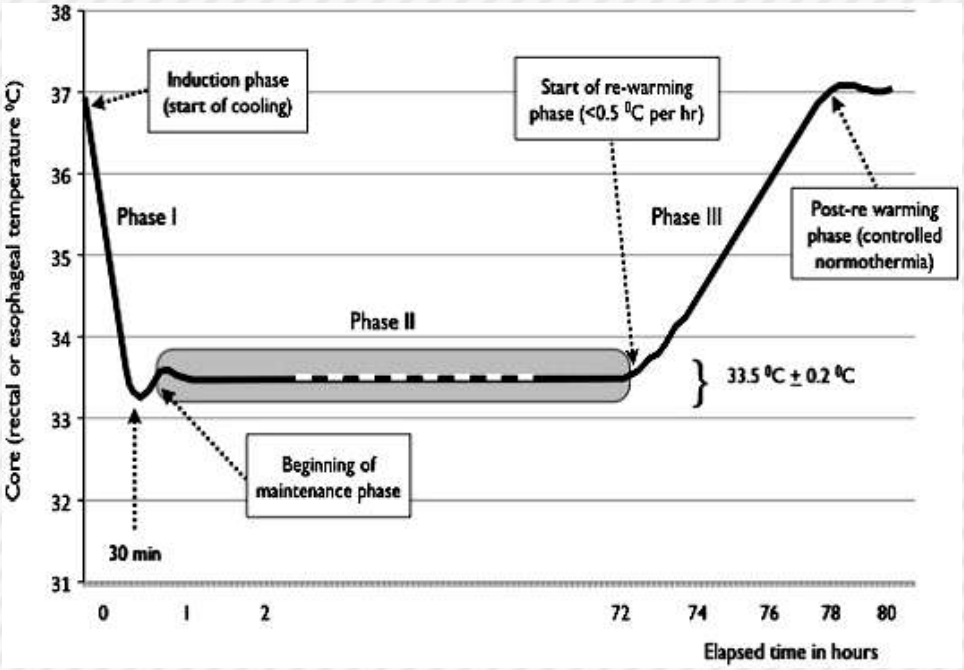
The ratio of inorganic phosphate (Pi) to phosphocreatine (PCr) is validated marker of mitochondrial function.

Brain metabolism is normal following resuscitation but deteriorates later



Azzopardi et al. Pediatr Res 1989;25:445-451

Hypothermia: concept



- To induce a stable central temperature around 33.5 +/- 0.5°C
- Before 6 hours of life
- In the most stable manner
- For a 72h duration
- Progressive and cautious rewarming 0.2°C / h

Hypothermia: cellular effects

- ↘ cerebral metabolism → ↘ edema
- ↘ energy utilization
- ↘ cytotoxic amino acid accumulation (glutamate) and nitric oxide
- ↘ platelet-activating factor → ↘ inflammatory cascade
- ↘ secondary neuronal damage and cell death
- ↘ extent of brain damage
- ↘ blood brain barrier dysruption

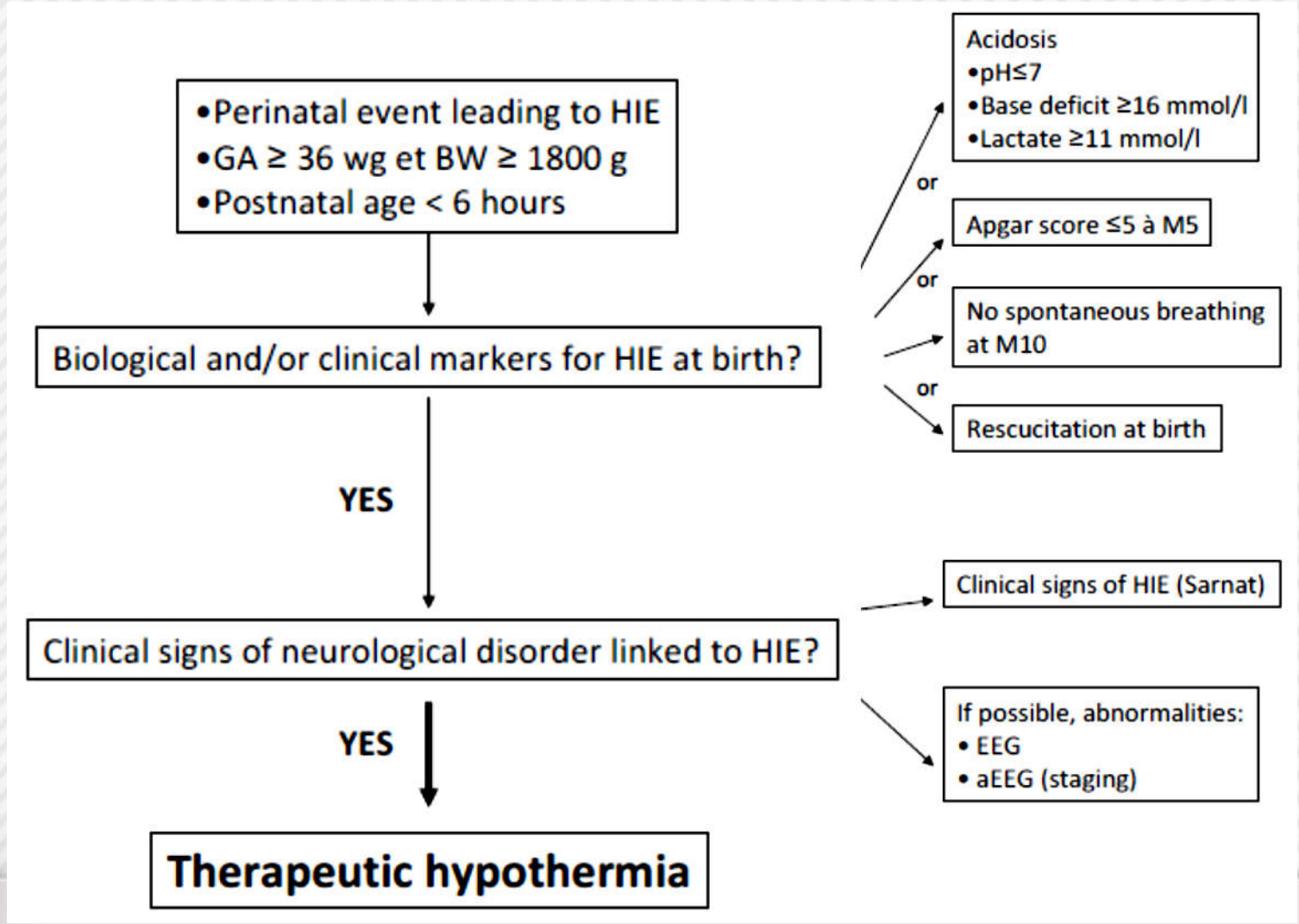
Experimental evidence supporting therapeutic hypothermia

- 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

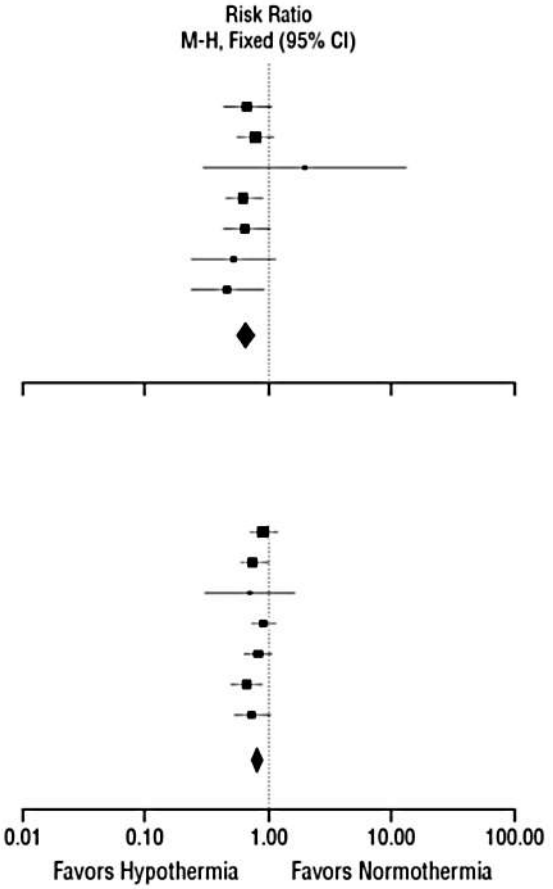
Head cooling or
total body cooling

Hypothermia criteria



Beneficial effect of hypothermia according to HIE severity

Study or Subgroup	Hypothermia Events	Hypothermia Total	Normothermia Events	Normothermia Total	Weight, %	Risk Ratio M-H, Fixed (95% CI)
Infants With Moderate Encephalopathy						
Azzoparadi et al,[13] 2009	20	65	30	67	17.9	0.69 (0.44-1.08)
Gluckman et al,[10] 2005	28	62	39	69	22.3	0.80 (0.57-1.13)
Gunn et al,[32] 1998	4	10	1	5	0.8	2.00 (0.30-13.51)
Jacobs et al,[20] 2011	26	61	34	51	22.4	0.64 (0.45-0.91)
Shankaran et al,[12] 2005	22	69	30	63	19.0	0.67 (0.43-1.03)
Simbruner et al,[21] 2010	6	19	9	15	6.1	0.53 (0.24-1.15)
Zhou et al,[22] 2010	9	41	19	41	11.5	0.47 (0.24-0.92)
Subtotal (95% CI)		**327**		**311**	**100.0**	**0.67 (0.56-0.81)**
Total events	115		162			
Heterogeneity: $\chi^2_6=3.75$; $P=.71$; $I^2=0\%$						
Test for overall effect: $z=4.27$; $P<.001$						
Infants With Severe Encephalopathy						
Azzoparadi et al,[13] 2009	54	98	56	95	26.8	0.93 (0.73-1.19)
Gluckman et al,[10] 2005	28	40	32	35	16.1	0.77 (0.61-0.96)
Gunn et al,[32] 1998	2	3	3	3	1.6	0.71 (0.31-1.66)
Jacobs et al,[20] 2011	25	30	24	27	11.9	0.94 (0.76-1.15)
Shankaran et al,[12] 2005	23	32	34	40	14.2	0.85 (0.66-1.09)
Simbruner et al,[21] 2010	21	34	39	43	16.2	0.68 (0.51-0.90)
Zhou et al,[22] 2010	22	38	27	35	13.2	0.75 (0.54-1.04)
Subtotal (95% CI)		**275**		**278**	**100.0**	**0.83 (0.74-0.92)**
Total events	175		215			
Heterogeneity: $\chi^2_6=5.12$; $P=.53$; $I^2=0\%$						
Test for overall effect: $z=3.46$; $P<.001$						

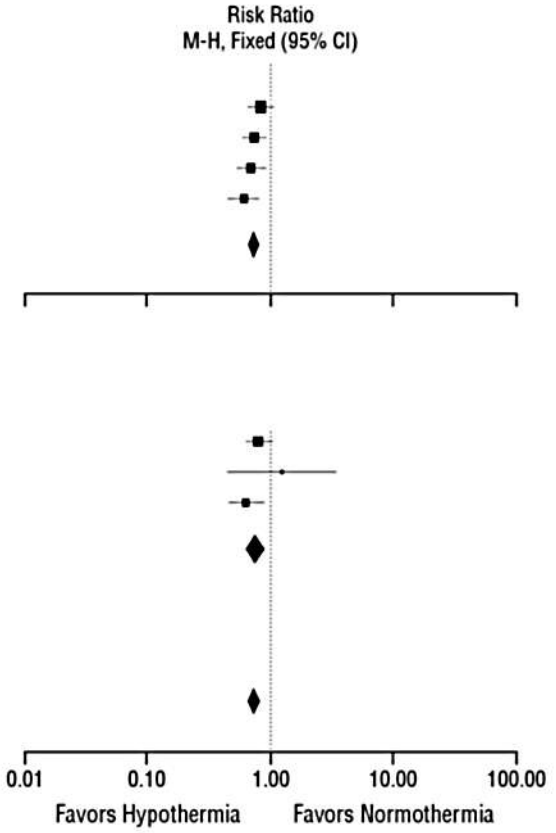


Tagin et al., Cochrane 2012

NNT 6-8

Beneficial effect of hypothermia according to coolling technique

Study or Subgroup	Hypothermia Events	Hypothermia Total	Normothermia Events	Normothermia Total	Weight, %	Risk Ratio M-H, Fixed (95% CI)
Total Body Cooling						
Azzoparadi et al,[13] 2009	74	163	86	162	22.6	0.86 (0.68-1.07)
Jacobs et al,[20] 2011	51	91	58	78	16.3	0.75 (0.60-0.94)
Shankaran et al,[12] 2005	45	102	64	103	16.7	0.71 (0.54-0.93)
Simbruner et al,[21] 2010	27	53	48	58	12.0	0.62 (0.46-0.82)
Subtotal (95% CI)		**409**		**401**	**67.6**	**0.75 (0.66-0.85)**
Total events	197		256			
Heterogeneity: $\chi^2_1=3.31$; $P=.35$; $I^2=9\%$						
Test for overall effect: $z=4.50$; $P<.001$						
Selective Head Cooling						
Gluckman et al,[10] 2005	59	108	73	110	18.9	0.82 (0.66-1.02)
Gunn et al,[32] 1998	7	18	4	13	1.2	1.26 (0.46-3.44)
Zhou et al,[22] 2010	31	79	46	76	12.3	0.65 (0.47-0.90)
Subtotal (95% CI)		**205**		**199**	**32.4**	**0.77 (0.65-0.93)**
Total events	97		123			
Heterogeneity: $\chi^2_6=2.35$; $P=.31$; $I^2=15\%$						
Test for overall effect: $z=2.79$; $P=.005$						
Total (95% CI)		**614**		**600**	**100.0**	**0.76 (0.69-0.84)**
Total events	294		379			
Heterogeneity: $\chi^2_6=5.79$, $P=.45$; $I^2=0\%$						
Test for overall effect: $z=5.29$; $P<.001$						
Test for subgroup differences: $\chi^2_1=0.06$; $P=.80$; $I^2=0\%$						

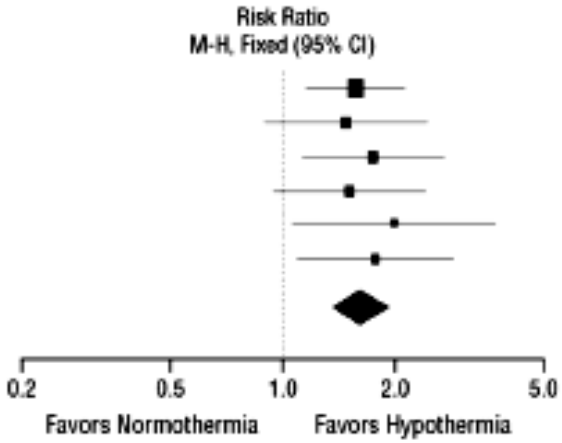


Tagin et al., Cochrane 2012

Normal outcome following hypothermia for HIE

Study or Subgroup	Hypothermia Events	Hypothermia Total	Normothermia Events	Normothermia Total	Weight, %	Risk Ratio M-H, Fixed (95% CI)
Azzopardi et al,[13] 2009	71	163	45	162	33.4	1.57 (1.16-2.12)
Gluckman et al,[10] 2005	29	108	20	110	14.7	1.48 (0.89-2.44)
Jacobs et al,[20] 2011	42	106	22	97	17.0	1.75 (1.13-2.70)
Shankaran et al,[12] 2005	32	102	22	106	16.0	1.51 (0.94-2.42)
Simbruner et al,[21] 2010	21	33	8	25	6.7	1.99 (1.06-3.72)
Zhou et al,[22] 2010	32	59	15	49	12.1	1.77 (1.09-2.87)
Total (95% CI)		**571**		**549**	**99.9**	**1.63 (1.36-1.95)**
Total events	227		132			

Heterogeneity: $\chi^2_5 = 0.91$; $P = .97$; $I^2 = 0\%$
Test for overall effect: $z = 5.35$; $P < .001$



Tagin et al., Cochrane 2012

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

Rutherford et al., 2009

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 Veries & Jongmans, 2010)

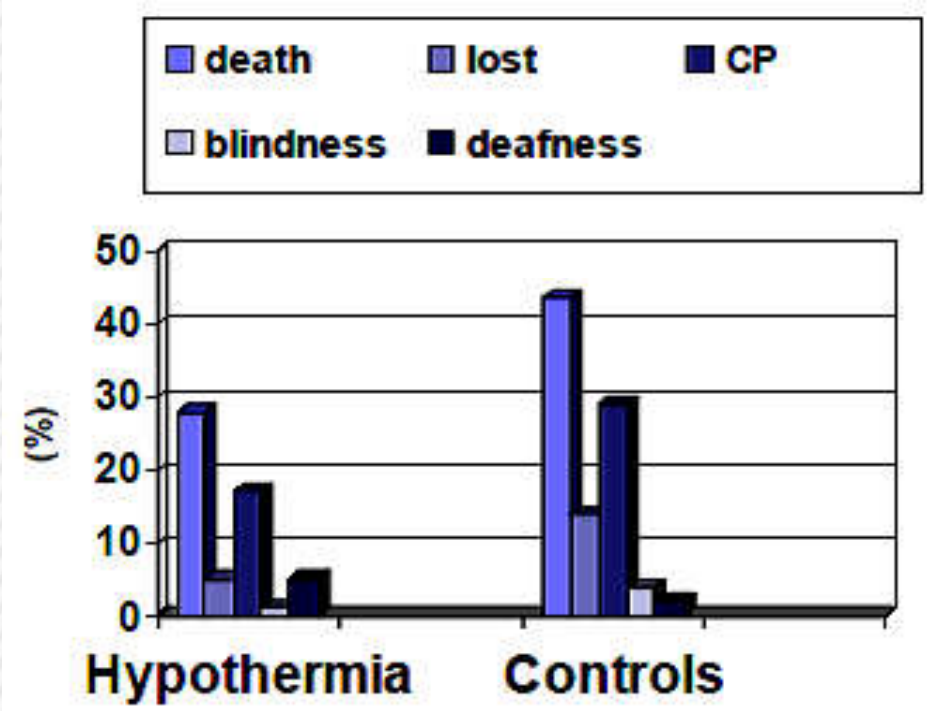
Childhood outcomes after hypothermia for HIE

- **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 (6y8m) vs 97 hypothermia (6y7m)
  - 18 lost (15% of surviving)
  - Motor : GMFCS / Intellect : WPPSI-III & WISC-IV / Attention, FE, Visuospatial: NEPSY / Emotional & Social : Child Health Questionnaire

Shankaran et al., NEJM 2012

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%)



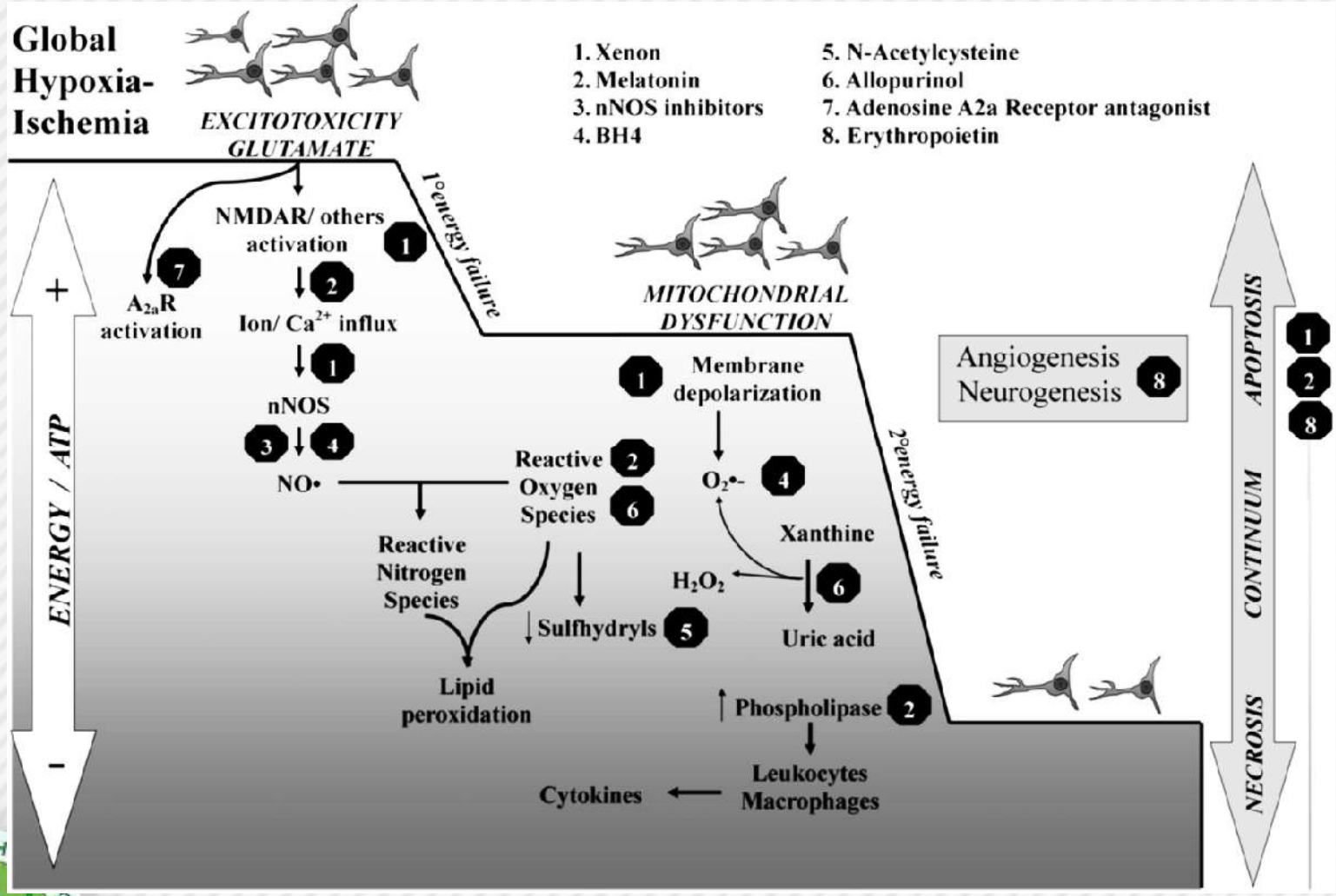
Shankaran et al., NEJM 2012

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 %)

Shankaran et al., NEJM 2012

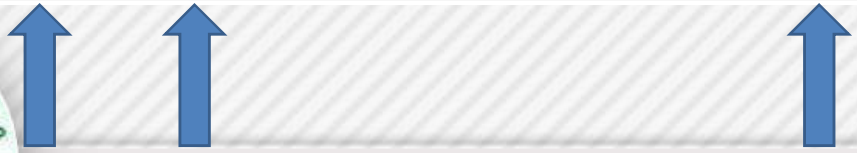
Hypothermia + neuroprotective agents



Robertson et al., 2012

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%)



Robertson et al., 2012

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)